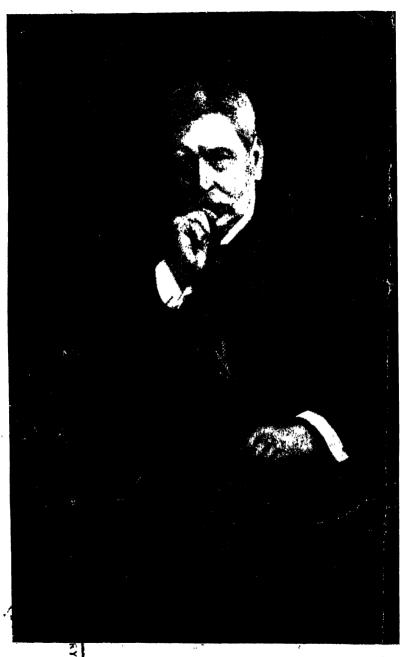
MANSON'S TROPICAL DISEASES



SIR PATRICK MANSON, G.C.M.G., F.R.S.

PLATE I

MANSON'S TROPICAL DISEASES

A MANUAL OF THE DISEASES OF WARM CLIMATES

EDITED BY

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Fourteenth Edition

WITH 15 COLOUR PLATES, 11 HALF-TONE PLATES, 414 FIGURES IN THE TEXT, 8 MAPS, AND 29 CHARTS



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PREFACE TO THE FOURTEENTH EDITION

THE publication of the fourteenth Edition of Tropical Diseases marks the eighth revision of the book for which the Editor has been responsible.

Perhaps the most important event since the publication of the last Edition has been the widespread application of the many so-called antibiotics to the treatment of tropical diseases, with gratifying results. Thus, it has come to pass that many diseases, such as plague and typhus, now respond favourably to treatment. Almost as remarkable has been progress in the treatment of leprosy under the influence of sulphones. The blessings which these advances bestow in relieving pain and alleviating the terrible disfigurements of this age-old disease are inestimable.

The undoubted success achieved by insecticides in the prevention of many tropical diseases has necessitated more space being devoted to this subject which has now achieved the importance of a separate science. In consequence of these measures malaria has been banished from some of its ancient haunts—surely one of the most meritorious and remarkable feats in the history of medicine. The recognition of a new nutritional disease—kwashiorkor—has warranted a new chapter on this subject, whilst it has been necessary to give an account of quite a new disease—epidemic hæmorrhagic fever—which has broken out in Korea.

The increasing accumulation of knowledge has entailed considerable revision and pruning in order to bring the book up to date and to make room for new material. It has therefore been necessary to jettison the chapters on diet and nutrition, whilst the preliminary statement on virus diseases and the historical sections in each chapter have had, regretfully, to be discarded. It is hoped, by so doing, that the standard of the new Edition, under stress of competing claims of various aspects of this very large subject, has been maintained; at the same time the Editor has endeavoured to ensure that no item of interest and importance to practitioners in the tropics and students of tropical medicine has been omitted.

PHILIP MANSON-BAHR

149, Harley Street, W.1.

January, 1954.

PREFACE TO THE FIRST EDITION

A MANUAL on the diseases of warm climates, of handy size, and yet giving adequate information, has long been a want; for the exigencies of travel and of tropical life are, as a rule, incompatible with big volumes and large libraries. This is the reason for the present work.

While it is hoped that the book may prove of practical service, it makes no pretension to being anything more than an introduction to the important department of medicine of which it treats; in no sense is it put forward as a complete treatise, or as being in this respect comparable to the more elaborate works by Davidson, Scheube, Rho, Laveran, Corre, Roux, and other systematic writers in the same field.

The author avails himself of this opportunity to acknowledge the valuable assistance he has received, in revising the text, from Dr. L. Westenra Sambon and Mr. David Rees, M.R.C.S., L.R.C.P., Superintendent, London School of Tropical Medicine. He would also acknowledge his great obligation to Mr. Richard Muir, Pathological Laboratory, Edinburgh University, for his care and skill in preparing the illustrations.

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TROPICAL DISEASES

CHAPTER I

PREPARATIONS FOR RESIDENCE IN THE TROPICS

GENERAL OBSERVATIONS

WHILE there can be no absolute standard of height and weight, the deviation from the generally accepted averages should not be great. As a rule, spareness is more desirable than plumpness. Certainly the tropics is no place for the fat man. The "lanky," spare type is best suited to tropical conditions, and the dark-haired, brown-eyed and dark-complexioned is generally considered more fitted than the blue-eyed, fair-haired, tender-skinned "Nordic" or "Aryan" type.

Teeth.—As the food in the tropics is neither so palatable nor so easily masticated as at home, teeth must reach a high standard, and candidates with carious teeth or defective enamel should be eliminated. Everyone who proposes to go to the tropics should have his mouth put in order, because dental decay takes place more rapidly in intense heat. There cannot be any objection to dentures if the owner possesses a spare set, and they are adequate and comfortable.

Nose and throat.—Special care should be directed to the tonsils. If they are enlarged and septic they must be enucleated. Subjects of post-nasal catarrh and chronic granular pharyngitis do not do well. Sinus trouble does not improve in the tropics and, for North and West Africa, where sandstorms are common, persons suffering from chronic antral disease should be refused.

Eyes and ears.—Reasonable visual acuity is essential. Opinions differ considerably on the extent of deficiency which may be passed over. The Editor is of the opinion that grave refractive errors are deleterious and, in certain circumstances, candidates with a degree of myopia above —6D should be rejected. No candidate with high myopia is suited for a bush or isolated station. If glasses must be worn, the wearer must have spare sets. Crookes's lemon-tinted lenses are of value in diminishing glare. In certain regions in the Sudan and Northern Nigeria, for instance, smoked glasses are a necessity to mitigate eye-strain. Normal colour vision is essential. Chronic conjunctivitis of all kinds is a distinct disability.

Middle-ear disease with discharge and aural eczema disqualify: both are made worse by tropical conditions. Perforation of the tympanum and any kind of deafness must be investigated. Deafness in more than a moderate degree is a bar.

Respiratory system.—Special attention must be paid to the lungs. Asthmatics and subjects of "hay fever" are quite unsuited for tropical residence, for, contrary to popular belief, asthma, hay fever, allergic rhinitis and, indeed, allergic conditions of all kinds are aggravated by the uxuriant vegetation, while flowering grasses and the pollen of rice and sugar-cane are very irritating. Sugar-cane fibre is often used for stuffing

pillows and excites asthma in susceptible individuals. The same applies to chronic bronchitis and emphysema. Any suspicion of tuberculosis, whether glandular or parenchymatous, calls for X-ray examination,

especially in candidates with a bad family history.

The Editor is strongly of the opinion that any candidate with a Ghon's focus, or any evidence of healed apical lesions, is quite unfitted for the tropics. Contrary to popular opinion, damp heat induces and fosters, but does not cure tuberculosis. Those who have calcified bronchial glands, and who have already thereby demonstrated their resistance to the disease, may, on the other hand, be considered suitable.

Cardiovascular system.—Any valvular heart disease is a contraindication. It is probably true that persons with mild degrees of mitral stenosis are not seriously inconvenienced by tropical life, but the increase in the metabolic rate and the strain placed upon the heart and respiratory organs by extreme heat has a deleterious effect upon the action of the heart. Of all heart lesions, acrtic requiritation, especially of luctic origin, is the most undesirable. Sinus arrythmia and extrasystoles are frequently encountered in tropical residents, and are not in themselves deleterious. Persistent tachycardia, from whatever cause, should be a bar to tropical service, and a candidate exhibiting a rapid pulse, which does not arise from nervousness during the medical examination, should be subjected to a searching exercise tolerance test.

Hyperpiesia.—Subjects of high blood-pressure are definitely excluded. Hyperpiesia, due to intrinsic hypertension or arterio-selerosis, is a serious handicap in the tropics. Often, in nervous young men, a high systolic reading may be obtained, and while this for the most part can be overlooked, a persistent high diastolic pressure above 100 mm. Hg is an absolute disqualification. Such persons inevitably break down after prolonged tropical residence; they are more liable to neurasthenic symptoms, and, in the Editor's experience, usually end up with cerebral hemorrhage.

Digestive system.—Nothing is more important than the digestive history. The organs of digestion are necessarily subjected to considerable strain; therefore subjects of nervous dyspopsia, hyperchlorhydria, or severe gastric disturbances, should not go abroad. A previous history of duodenal or gastric ulcer, especially where confirmed by radioscopy, should debar a candidate, especially from places characterized by damp heat, such as the west coast of Africa or Malaya. It must be remembered always that, even under the best circumstances, a great deal of the daily fare consists of frozen or tinned food.

If the indigestion is due to chronic inflammation of the appendix, it is most important that appendicectomy be performed before sailing. It is obvious that, for many reasons, appendicitis may be a much more dramatic and important event than under more highly civilized conditions.

Persons of a "bilious" or a hepatic tendency, with lustreless skin and a jaundiced look, withstand the tropics badly; therefore any palpable enlargement of the *liver* must be noted. Splenonegaly may, occasionally, denote previous attacks of malaria, and indicate that the candidate is hypersensitive to this infection or, on the other hand, it may mean that he has some obscure blood disease, and is therefore unsuitable.

Sufferers from chronic colitis are ruled out. A history is not always easy to obtain; but if there is any previous account of blood or mucus in the stools, or both, or pain on defæcation, or any suspicion of ulcerative colitis, the matter must be investigated. This disease is so liable to remissions that the candidate may appear well and healthy at the examination, but relapses under tropical conditions are apt to be especially severe. The peculiarly sensitive type of person who is colon-minded, and subject to mucous colitis and spastic colon, does badly and cannot be recommended. Subjects of diverticulitis fare badly also, and, if this condition is detected as a cause of abdominal discomfort in a more elderly subject, tropical service is not recommended. Any history of gall-bladder disease should debar the candidate, owing to the risk of developing cholecystitis and biliary calculus under tropical conditions.

Hæmorrhoids. Piles are a curse of life in hot climates where those predisposed to the disorder almost invariably become sufferers. They should be removed surgically, as injection methods do not appear to be

altogether satisfactory.

Hernia.—Candidates with inguinal herniæ of any description must submit to operation before going abroad. Trusses, even of the lightest variety (celluloid), are most inconvenient, and are apt to cause intertrigo and skin irritation. The same applies to umbilical herniæ; pads cannot

be worn and are usually inefficient.

Genito-urinary system.—Renal and vesical calculi are more likely to develop in the tropics than in temperate regions. No one with a history of renal colic should be accepted. Black (1945) states that oxaluria was very common in British troops in India during the hot season. This is ascribed to the loss of body fluid by sweating, inadequate fluid intake and the presence of oxalate-forming food in the diet. There appears to be some connection with amorbic dysentery. Microscopically the crystals may be in the octohedral or envelope form, dumb-bell or biscuit shaped. A combination of oxaluria and hæmaturia may be the direct precursor of calculus formation. Therefore oxaluria should be considered as debarring from tropical service. Enlarged and palpable kidneys may indicate congenital cystic disease, which is a disqualification. Special attention must be paid to the urine. Moderate degrees of albuminuria (physiological or postural) are extremely common in athletic and otherwise healthy young men, and the Editor is of the opinion that it is quite unfair to reject a suitable candidate merely on this account. It is different when there is an appreciable amount of albumin (5 per cent.). Numbers of casts in the deposit indicate a predisposition to severe renal disease. Sugar in the urine, however, is somewhat different. If a very considerable precipitate is obtained with Fehling's and Benedict's solutions, then a blood-sugar curve estimation must be done. No diabetic ought to be passed for service in the tropics unless he can be kept under strict supervision. Opinions vary about renal glycosuria. If the candidate has a low sugar tolerance with a low renal threshold for glucose, he is best out of the tropics, as the condition may possibly predispose to true diabetes.

The cellular deposits of the urine should always be examined. Subjects of phosphaturia, so-called "phosphatic diabetes," owing to the

concentration of urine which occurs in a hot climate, are unsuitable. Those showing evidence of *Bact. coli* or streptococcal infection must be rejected. A constant source of trouble is urinary tuberculosis, on account of the difficulty of detecting the tubercle bacillus; but when large numbers of pus cells are present in the urinary deposit without other ascertainable cause, tuberculosis should be suspected and the candidate rejected. Chronic genorrhæa and chronic prostatitis are always a source of trouble and a reason for rejection.

Female candidates.—Among women, disorders of the genital organs tend to dominate the picture. Since impairment of the menstrual functions is usually aggravated by tropical residence, the menstrual history must be carefully investigated. Those inclined to dysmenorrhea or menorrhagia should be forbidden, if possible, to go out. Subjects of periodic amenorrhea suffer more in the tropics, and the same may be said of uterine displacements. Women who are predisposed to miscarriage are more liable to this accident under the less civilized conditions of the tropics.

Minor vaginal or uterine disabilities, such as vaginal discharges, may be overlooked. Women in advanced pregnancy should not attempt to go out, and it is advisable that a primipara should not proceed to a hot climate in the middle of her pregnancy.

Integuments.—Special attention must be paid to the skin, hair and nails. Alopecia is apt to progress under tropical conditions. Cracked and brittle nails indicate a feeble constitution. Clubbed fingers may indicate cardio-pulmonary disease, or may be merely a congenital deformity. Anyone with an abnormal skin must be specially investigated. It must always be borne in mind that the skin, as an organ of elimination and metabolism, is much more important in tropical than in temperate countries. Subjects of deficient sweating (anidrosis), unable to sweat freely, not only suffer acute discomfort but are in danger from heat stroke and heat exhaustion. Therefore, candidates having dry skins (xeroderma) and ichthyosis should be rejected. On the other hand, individuals whose sweat-glands are abnormally active do well.

Septic spots on the skin of the back and chest are frequently encountered in young men and, though each case should be judged on its merits, it must be remembered that residents in most tropical countries, but especially in West Africa, are particularly liable to septic infections, especially boils, so that anyone who is specially susceptible to the staphylococcus should be considered unsuitable.

Pscriasis is always a difficulty. Milder degrees may be passed over, and as a general rule are apt to disappear in very hot countries. Extensive pscriasis, however, especially when associated with suppuration, should debar from the tropics.

Acne.—Mild acne is usually improved by heat, but McLaughlin (1945) found that pustular and cystic forms of acne are aggravated by tropical service and that this form of eruption may develop in hot climates.

Eczema of all kinds is a distinct disability and so are sensitive, allergic skins, and those liable to intertrigo.

Central nervous system.—Nervous control is of paramount importance in the tropics. All exhibiting neurotic and hysterical tendencies should be rejected. *Epilepsy* is not always easy to detect, but epileptics must on no account go out. Any chronic affection of the spinal cord, e.g., Friedreich's ataxia or spastic paraplegia, is a disqualification, as is a previous history of encephalitis lethargica or cerebro-spinal meningitis.

A candidate has sometimes suffered from infantile paralysis. If it merely affects one limb, and the muscular atrophy is not too extreme, he may be passed, though it must be understood that the tropics is no place for a cripple. Exaggerated deep reflexes and tremors of hands or tongue denote that the candidate has an unstable nervous control, and that he is unsuitable.

Anæmia.—Persons with anæmia which cannot be adequately explained are usually in poor health; they are "below par," and this suggests that they are lacking in vigour, energy and initiative. The pale young man or the sallow woman is unsuited for tropical residence. The hæmoglobin content is probably more important from this point of view than the red-cell count. Secondary anæmia usually indicates some underlying condition. It may be digestive, pulmonary, or even cardiac. Pale faces become paler still in the tropics, and the condition is more likely to progress there.

Affections of the thyroid.—The possibility of hyperactivity or insufficiency of the thyroid gland has to be kept in mind. The Editor is convinced that all thyroid tumours, whether adenomata, cystic adenomata or thyroid hypertrophy, are definite contra-indications to tropical service. The form of hyperthyroidism (usually due to substernal thyroid) which, though not leading to exophthalmic goitre, yet produces thyrotoxicosis with a special strain on the cardiac muscle, is particularly to be feared. The thyrotoxic heart is apt to be produced by exposure to tropical conditions, and may progress unchecked and end fatally. All degrees of hypothyroidism are also unsuited to tropical conditions.

Other endocrine disorders.—Endocrine disorders, such as hyperpituitarism, hypopituitarism, "Fröhlich's syndrome," achondroplasia,

and developmental anomalies, are to be excluded.

Gout and rheumatic arthritis.—A gouty diathesis is occasionally seen in comparatively young people, and may manifest itself in many ways. Gout may actually be provoked or aggravated by tropical conditions, and therefore must be regarded as a contra-indication. There is a popular idea that rheumatic affections of the joints are improved by exposure to heat, but this is far from true. Usually they are aggravated. The same is true of fibrositis.

Other disabilities.—Even such minor blemishes as the state of the feet must be inquired into. Deformities, club foot and hammer toes, in those who may be called upon to undertake long marches, may be held to be distinct disabilities. Fungus infection of the feet is particularly intractable under tropical conditions.

Preparations before sailing.—All those who are proceeding to the tropics and subtropics, whenever they come into contact with native servants, and whenever they mix with the native population, or whenever

they are forced to live in less sanitary surroundings than they have been accustomed to, should be inoculated about four weeks before departure against typhoid and paratyphoid (T.A.B.) (see p. 322). Anticholera and antityphus inoculations, which are routine in the Services, may be necessary for those who are going out to the countries where these diseases are endemic. They should also be revaccinated (one mark), if this has not been done within the three previous years. Very often this vaccination may not cause any obvious reaction, or in popular language, may not "take," but it must be attempted none the less. The vaccination may be conveniently performed at the same time as the second inoculation. If for other reasons, such as business matters or preparing for departure, circumstances prevent this, both inoculation and vaccination can be given on board ship if the voyage is long enough, e.g., the journey to India. Allowance must be made for any possible reaction. Thereafter it should be the rule to repeat the vaccination every five years and the inoculations every three years. Those proceeding to the West Coast or other parts of Africa, and to South America, where yellow fever is endemie, are strongly urged to be inoculated against this disease (see p. 358). It must be emphasized that out of the many thousands who have now been protected only a very few have contracted yellow fever, and it is now compulsory for all passengers flying to any part of Africa. The immunity produced lasts for four years.

PHYSIOLOGICAL EFFECTS OF A HOT CLIMATE

Body temperature.—On passing from a temperate to a tropical climate, a slight rise in body temperature occurs, rarely exceeding 1.5° F., and, after arrival in the tropics, the body temperature of the newcomer remains slightly elevated. In fully acclimatized Europeans it settles down to normal, but tends to rise after severe exercise. Breinl found the rectal temperature to be 101° F. (38.3° C.) on really hot days. Renbourn and Bonsall (1946) have found a higher mean temperature of Europeans in tropical climates. By using an ordinary clinical thermometer, with oral and rectal temperatures in Indian and British troops, higher levels were recorded than those generally accepted as normal. Oral temperatures up to 100.6° F. and rectal temperatures up to 101° F. may be recorded in apparently normal individuals. A significant correlation coefficient is not always found between resting oral and rectal temperatures. Exercise in the sun may cause a fall in the oral temperature.

Low fever.—Low fever is the term given to a little understood clinical picture, which is known by this vague description all over the world. It is characterized by lassitude, debility, and a long-drawn-out slight rise of temperature, which is frequently seen in children. Very little has been written about this condition in textbooks, but all are agreed that, in spite of the most searching bacteriological and biochemical tests, no specific organism can be held responsible. If low fever cannot be assigned to constipation, latent malaria, annebiasis, closed tuberculosis or genorrheal prostatitis, then it is certainly due to climatic causes, and probably "climatic fever" would be a better term. Most people become acclimatized to heat, but there are some whose heat-regulating mechanism cannot adjust itself fully; it is in these that climatic fever is seen. The temperature seldom rises above 100° F. at the hottest period of the day; but the most noticeable feature is that the daily minimum is raised the same amount as the maximum. The daily variations remain the same as before, but the entire level is shifted upwards. Some of these patients feel thilly at times, and during

these spells are most uncomfortable. Occasionally, too, there are periods of excessive sweating.

Skin reaction.—The regulation of body temperature is effected by evaporation of water from the surface of the body and from the lungs. It has been shown on a white skin that the temperature falls with the appearance of perspiration, and the greater the degree of perspiration the greater the fall of temperature. A brown or black skin absorbs more heat than the white skin, and the point where perspiration shows itself is reached earlier in the brown-skinned, showing that the cutaneous heat-regulating apparatus is more sensitive than that of the white man. In especially sensitive skins a particularly irritating form of urticaria—solar urticaria—has been described. A certain protection is given to skin sensitized to sunlight by the use of a cream containing quinine, ichthyol, or disodium naphthol sulphonate.

Respiratory exchange.—The cooling process is brought about by evaporation of water from the lungs. This is also to some extent effected by the attraction of the blood to the surface of the body. The place of the blood thus transposed is taken by air, and this is one of the reasons why the lungs weigh less in hot than in cold or temperate climates. The lung capacity is increased, and thereby the respiratory rate lowered.

Urinary excretion.—The excretion of urine is diminished with excessive sweating. The daily output of a normal adult in the tropics is 500-600 ml., as against 1,500 ml. in temperate countries. The urine is concentrated, but apparently contains the same amount of waste material as that found in 1,500 ml.

Blood.—The effect of what is termed primary adaptive reaction falls mostly on the blood. Vaso-dilatation comprises a rise of temperature of the part, transudation of fluid through the vessel wall into the tissues, increase in the insensible perspiration and in the amount of sweating, visceral vaso-constriction and blood dilution. Dilution of the blood is an early phenomenon which is succeeded by the opposite process when there is fluid loss from sweating. Investigations made in Java, the Philippines, Queensland, West Africa and Iraq indicate that climate alone produces no change in the formed blood elements, except a shift of the Arneth index to the left (see p. 1077). Nor does it produce any change in the hæmoglobin content or the specific gravity of the blood. De Langen and Schut in Java asserted that in the newly-arrived European the blood sugar is augmented; or, at any rate, there is a rise in the fasting level. On the other hand, Sundstroem concluded that the endocrine glands in the tropics exhibit a decrease of functional activity and that, therefore, a parallel decrease in blood sugar should take place. He found this in European individuals of both sexes who had lived in the tropics since birth. A positive correlation, moreover, was found to hold between the sugar values and the lecithin and cholesterol ratios of the blood.

The non-protein nitrogen, on the other hand, was about 25 per cent. higher than the standard average, but the urea, uric acid and total creatinin were normal. It is thought that endogenous and exogenous toxic substances, usually excreted by the kidneys, may be retained, and possibly predispose to the greater susceptibility to nephritis in a tropical climate. The phosphorus content of the whole blood was found by Sundstroem to be normal in individuals who had spent less than one year in the tropics, after which it dropped to 9 mgm. per 100 ml. for men, and 7 mgm. for women. Various suppositions are advanced to explain the diminution of blood phosphorus in the tropics. It is thought that a climatic stimulus may temporarily throw an excessive load on the mechanisms which supply phosphorized material for anabolic processes. The content of total fatty acids in the blood of tropical residents appears to be considerably lower than the

available standard figures for cooler climates, and this is thought by de Langen to explain the rarity of gall-stones in Malays and Javanese.

Digestion.—At first, as every traveller will testify from experience, there is a stimulation of appetite, as well as of the digestive function, but this is a passing phase, and is soon replaced by a diminution of appetite and a lowering of the digestive capacity, together with a diminished desire for animal food. Diarrhea and loose stools are almost invariable on first exposure to tropical conditions, and are soon followed by constipation. These "climatic diarrheas" are probably due to chills. Those subject to them should wear a woollen binder and avoid eating fruit, such as mangoes. Whenever an attack threatens a preliminary aperient, such as a tablespoonful of castor oil, should be followed by 10–15 drops of chlorodyne in water.

Circulation.—Exercise and humid heat produce a rise in blood-pressure, and also in the pulse-rate (Breinl). The average systolic blood-pressure shows a tendency to fall concomitantly with profuse sweating. The diastolic pressure closely follows the systolic.

Nervous system.—On the nervous system the first effects are those of stimulation, followed by depression, and when the latter is prolonged a neurasthenic state with loss of memory ("West Coast memory") is produced. In tropical residents of long standing there is an exaggeration of the deep reflexes, tachycardia and, eventually, insomnia and abnormal reaction to stimuli, which indicate a loss of control by the higher centres, and result often in unreasonable mental irritability. Electrical conditions also powerfully affect the nervous system. Among European children, especially, the whole nervous system appears to be in unstable equilibrium, resulting in fretfulness, peevishness and often in frank hysteria.

Generative functions.—In both sexes there is at first a stimulation of the sexual libido, but excess is soon followed by exhaustion, and often by sexual neurasthenia. In children, puberty is attained at an earlier age, so that in European girls menstruation commences about a year earlier than in temperate climates, but the onset of the menopause is not retarded.

Growth.—Growth in children is rapid, and they are usually under weight and lacking in physical strength. European children brought up in the tropics are generally described as "weedy."

Acid-base equilbrium and basal metabolism.—Sundstroom and Radsma are the only authorities who have carried out much work on these problems. The former finds that, as a rule, the alveolar carbon dioxide tension is lowered in the tropics. An alkalosis is present in the majority of tropical residents at the height of the hot season, and may have an undesirable effect on physical well-being. It is suggested that adequate water intake and muscular exercise may prove effective in combating this tropical alkalosis. Disturbances of endocrine function have an important effect on energy metabolism. Sundstroom found that the basal metabolism varied between 25.5 and 36.1 calories, with an average of 31. Variations in the dry- and wet-bulb temperatures may affect the level of basal metabolism in certain individuals. Radsma concludes that the basal metabolism in Europeans is reduced, or is, at least, lower than the standard values which obtain in Europe and America.

Perspiration.—Adaptation to high temperatures involves an increased capacity to produce sweat, a greater sensibility of the temperature regulatory apparatus, and, probably, a power to limit salt loss. In failure, such as that due to excessive salt loss, or to a steadily rising temperature, the sweat glands may be at fault. Anyone who is exposed to high temperatures should take

warning if a degree of exhaustion increases with each day of work, and if his

degree of recovery decreases with each night of rest (Dill).

Sweat varies in composition, depending upon its rate of production. In very hot weather, salt depletion is high, not only because of the large volume of sweat produced, but because this sweat is unusually high in salt content. While the glands excrete lactic acid, it is believed that this is not wholly dependent upon muscular exercise.

Thirst.—Thirst does not necessarily depend on a dry mouth, nor does it depend on the volume of blood plasma, or of the extracellular phase of other tissues. It depends upon the diminished water content, and possibly upon increased osmotic pressure of body cells. While thirst may be somewhat alleviated by rinsing the mouth, it can be satisfied only when water has been delivered by the blood-stream to the tissue cells demanding it (Dill).

PATHOLOGICAL EFFECTS OF TROPICAL CLIMATE

Tropical heat produces in fair-skinned people a characteristic pallor, sometimes with a yellowish discoloration of the skin. This tropical pallor, so commonly seen in Europeans long resident in India, has to be distinguished from tropical anæmia. The appearance of anæmia in these people is due to blanching of the skin, from thickening of the surface layer and increased pigmentation.

The tropical light produces effects in the skin, which may be acute or chronic. They range from a slight sunburn to a severe erythema, accompanied by blisters and cedema, so that a reaction may set in produced by septic absorption. Sometimes this may be so severe as to produce delirium, or even coma. Chronic skin irritation is shown by pigmentation and by vasomotor changes; that this is a process of natural selection is demonstrated by the skin pigmentation of most native races, so that the nearer the equator, the darker the skin, whilst that of a European long resident in the tropics tends to darken. When slight pigmentation is established, probably as the result of increased blood supply, hair and nails grow more rapidly. Freckles—small brown pigmented macules—are specially apt to occur in sandy, red-haired, or fair children brought up in a tropical climate, and are often very disfiguring. Chronic solar dermatitis, or sailor's skin, especially at the back of the neck, is characterized by atrophy, wrinkling, pigmentation, white atrophic patches, telangiectases and warty growths (solar keratoses), some of which, especially when situated on the dorsum of the hands, eventually become the seat of basal (rodent ulcer type) or squamous-celled neoplasms.

Summer eruption is a polymorphic eruption of erythema papules, vesicles, weeping areas, crusts, pigmented macules and small depressed scars, which occurs

in exposed parts, especially among children.

Urticaria is occasionally produced by the actinic rays. Xeroderma pigmentosum (Kaposi's disease) is a congenital condition of light-sensitiveness, such as is produced by X-rays on a normal skin. This manifests itself by pigmentation, telangiectasis, keratoses, and finally epithelioma, and is produced by the ultraviolet region of the spectrum. It is said to be more frequent in the tropics than elsewhere. Cheilitis actinica is a condition of the lips caused by burning by ultraviolet light at high altitudes in S. Anatolia. Secondary carcinoma often results. The effect of tropical sunlight on the eyes is well known to produce glare conjunctivitis, necessitating smoked or tinted spectacles. Pterygium, or a triangular fibrous growth extending over the conjunctiva to the pupillary margin with its base towards one or other canthus, is common in tropical residents, and is considered to be a natural reaction to intense sunlight. Œdema of feet and legs in young adults is frequently noted on first entering a tropical climate. It is of

cardiovascular origin and is probably an indication of the adjustment of that system to new conditions. This cedema passes off on acclimatization.

The congestive disorders, affecting especially the liver and bowels, are probably due more to sudden changes of temperature. The concentration of the urine predisposes to gravel and probably accounts for the frequency of renal and vesical calculi in tropical residents, especially in hot dry climates, such as that of the plains of India and the arid districts of the Sudan and Northern Nigeria. People living in hot, dry climates with an inadequate water supply may suffer from backache or even renal colic, probably due to deposition of salts in the renal pelvis or ureter. It is evident that, where fluid loss is so great, exceptional intake of fluid becomes necessary.

Insect bites. Newcomers to the tropics, women in particular, are very sensitive to effects of insect bites, especially those of mosquitoes. These attack usually at sundown and in the night hours and commonly bite through mosquito netting when a part of the body, buttocks, legs or arms are pressed against it. The irritation of the stings is caused by injection of the insect's saliva. The reaction varies greatly in different individuals. The redness and ædema are due to libration of histamine in the tissues. Irritation and itching can be relieved by the application of Scrubb's ammonia, tineture of iodine, Reckitt's blue, but, under modern conditions, by anti-histamine preparations—a number of which are now procurable. A good antidote is Thephorin ointment (Roche). This contains 5 per cent. of active substances in a simple water-miscible base of polyethylene glycols. It should be applied to and rubbed into the site of the bite, or bites, at frequent intervals. Thephorin is phenyl-methyl-tetrahydroaza-fluorine hydrogen tartrate.

Mosquito and other insect repellents are described under malaria, trypanosomiasis and other insect-horne diseases

CHAPTER II

LIFE IN THE TROPICAL CLIMATES AND GENERAL DISEASES OCCURRING IN THE TROPICS

CLOTHING AND GENERAL HYGIENE

THE sun helmet (or topee) should be white or khaki and have a dark or green lining and is known as a solah topee. This is no longer considered as essential for protection against the sun and has now been discarded by the military authorities. A soft felt hat, such as the "double Terai," is the best all-round headgear. During the 1939-1945 war a felt hat with an exaggerated brim of the "Buffalo Bill" type was much the most useful and stood up to all kinds of weather and did not become pulped in the rain as does the more cumbrous topee. The deleterious effects of the sun's rays on the cranium have been proved to be mythical. To prevent glare, and to mitigate the effect of light—as some believe that the ill-effects of the solar rays are exercised through the eyes-smoked or tinted glasses should be worn.

Clothing should above all be loose, especially around the neck and chest. The fabrics usually worn are white or light-coloured, and cotton is best. A light flannel shirt is popular. Whenever washable trousers or shorts are not used, light cotton or calico drawers should be worn for the sake of cleanliness and to prevent irritation. A backless waistcoat should be worn in the evenings. Where a coat or tunic is not worn, a spinal pad of dark material is very useful, and a strip of cotton sewn inside the shirt answers the purpose very well. Experimental work in the Philippines has shown that white or khaki are the best colours for external clothing in their power of reflecting heat. Khaki is preferable for thin clothing. White drill is stiff and not well ventilated; tussore silk is better, but expensive. Most experienced travellers agree that the lighter the clothing, the better. Shorts are universally worn by men and, once the skin of the knees has become used to the sun, they have many advantages, the chief disadvantage being that they expose an extra skin area to mosquito bites. This, however, can be avoided by flaps which can be turned down under the puttee or legging. The provision of slits under the armpits of shirts and tunics is advisable.

The "cholera belt," a popular mode of protecting the abdominal wall against chills, has been the subject of much criticism. Modern opinion, though condemning the wearing of a woollen belt during the ordinary times of the day, considers such a protection indispensable when sleeping near a draught. The best protection is to wrap a broad binder or a towel, preferably of wool, round the waist. The experience of naval officers during the recent war has revived interest in this ancient question. Kershaw (1947) has proved that non-specific enteritis, or even mild dysentery, can be traced to chill. It is common knowledge that chilling of the abdomen by rapid ingestion of large quantities of cold water or ice-cream, when the body is heated, gives rise to violent diarrhoa. Even the wearing of a wet bathing costume, whilst sun-bathing, may do the same. Observations on warships have shown that the plenum system of ventilation at night is the cause of acute abdominal pain, colic and diarrhea. Men who sleep in hammocks are more liable than those in camp beds. Prophylactic measures consist of wearing a bush-shirt, or a loose-fitting shirt, with a cellular undervest. A change to thicker clothing should be made towards sundown. Cool drinks should be sipped slowly and sitting in direct draughts must be avoided.

Boots call for careful selection and should be half a size larger than those worn in temperate climates, as the feet swell readily in the heat. The coolest material for "uppers" is white canvas. Rubber-soled shoes are liable to "draw" the feet. It is well to have a pair of gum boots for the raius and for use at night. "Mosquito boots" are long boots of thin white canvas or light soft leather.

Women's clothing in the tropics.—As far as possible women's clothing should be made of fine, soft material. It should consist of vest and knickers, which may have to be changed two or three times daily to prevent prickly heat. A loosely-woven cotton gauze, or a mixture of cotton with silk or wool, are best. Stockings, if worn, should be of cashmere, but bare legs are better. A white umbrella, or parasol, lined with green, is almost a necessity.

Children's clothing in the tropics.—Children's garments should be soft, light and loose. In very hot weather cotton gauze is best for underclothing, as the sensitive skin is very liable to prickly heat.

Food.—Large quantities of food are not well tolerated, though possibly this may to a certain extent be attributable to monotony. The diet should consist of foods which produce a minimum of heat. Of the true essential constituents, fats and oils have the highest caloric value, hence the almost instinctive aversion of Europeans to greasy and fatty foods in a hot climate. There is usually, also, a distaste for animal food, a fact which, to a certain extent, is explained by the poor quality of meat obtainable and the lack of variety in cooking, but it is true that excessive meat-cating is harmful, probably on account of incomplete digestion, unless the body is being actively exercised. This is true for most tropical countries which have a cool season, such as the Sudan or Iraq. Meat can safely be eaten in the cold weather.

Generally speaking, the indigenous products of tropical countries are more suitable for food than any which can be imported. Sugar is a very valuable constituent of the diet in the tropics, especially for Europeans on the march, or on safari. Preserved dates and figs therefore have acquired a reputation among travellers, and it is wonderful how sustaining they prove, provided that the requisite quantity of liquid can be procured at the same time.

Breast-fed infants thrive as a rule, and it is said that the quality of the milk of European mothers is usually not impaired by tropical conditions. Most women, however, cannot stand the strain of nursing their babies for any length of time. In Panama it has been found that the average milk of the coloured woman foster-mother is richer than that of the European, and often upsets the digestion of the child, and in most parts of the tropics babies must be artificially fed. Cows' milk being very rarely obtainable, it is necessary to use prepared foods, such as Mellin's, or condensed milk. Banana flour is an excellent food for infants.

Beverages.—An ample supply of water is vitally necessary, and the amount varies according to the climate. During the hot weather in the Deccan in India, where the percentage of moisture is very low, it was found by Hunt that Europeans who lived in tents and took a good deal of exercise required no less than three gallons of water per head per day. This was also recognized during the 1914-1918 war, in Iraq, where it was laid down that even a greater quantity than this might be needed under the conditions that prevailed. Even with this supply the exerction of urine was by no means excessive. As much as 1-32 gallons is required to neutralize the heat produced by metabolism, quite apart from the heat added to the body by radiation and conduction. This holds for dry climates, with a high dry-bulb temperature, but in still, moist atmospheres, where evaporation is at a minimum, imbibing large quantities of fluid merely increases the discomfort.

Alcohol.—Widely differing opinions are expressed about alcohol. By some -and it may be said the great majority-it is deemed a necessity and consequently beneficial, whereas by others, except for the old and infirm, it is regarded as a luxury and superfluous. Be that as it may, a moderate amount of stimulant, reserved as a "sun-downer," probably does no harm, reviving the flagging energy and lending some colour to an otherwise monotonous day. It is probable that the average healthy adult male can deal satisfactorily with 13 oz. of alcohol daily. Alcohol taken with the evening meal promotes good fellowship, stimulates the appetite and aids digestion, but the inevitable whisky and soda between meals is to be discouraged.

Aërated drinks are universal, and are useful in aiding digestion. "Frigidaire," by providing cooling drinks, which are beneficial in relatively small quantities, has done a great deal towards the promotion of cornert health in tropical countries.

SOME GENERAL DISEASES OCCURRING IN THE TROP attacks of aphtha-like lesions in the mouth and on the geninella combined with ocular changes. It is a long drawn-out chronic disease and some fourteen cases have been reported. In smears from the lesions elementary bodies were found and when stained by Giemsa resembled Paschen bodies of variola. Ocular changes are hypopyon iritis and additional symptoms are erythema nodosum lesions, acneiform or papulopustular eruptions. Death may take place from cerebral attacks when multiple inflammatory foci are present in the brain (Berlin, 1944).

DISEASES OF THE DIGESTIVE SYSTEM

Little is known about variations in gastric secretion in the tropics, save that in ancylostomiasis and other worm infestations the secretion of hydrochloric acid by the oxyntic cells is reduced; but it is a striking fact that gastric and duodenal ulcers are seldom encountered in native races living on a simple carbohydrate diet. This applies especially to Indians, Javanese and Negroes. As the result of 2,170 autopsies, Kouwenaar in Java concluded that ulcers of the stomach and duodenum are found only in 1 per cent. of Javanese as against 10 per cent. of Chinese, but they are said to be very common in Abyssinians, and this fact is ascribed to dietetic causes (Bergsma). Wanless finds them common in rural districts of western India, due to septic mouths and excessive stimulation by hot curries. Diverticulosis and diverticulitis appear to be very rare or almost unknown.

APPENDICITIS

Inflammation of the appendix is rare, and fulminating cases requiring immediate operation seldom occur in native races, in marked contrast to the frequency of this condition in European residents. In Indians, both Moslems and Hindoos, acute appendicitis is extremely rare and the Editor has seen only two cases in over thirty years.

Volvulus of the small intestine, part or whole, is the commonest cause of intestinal obstruction in African natives (Kerr and Kirkaldy-Willis).

It occurs between 25-40 years. The chief complaint is abdominal pain and tympanites; vomiting is not a feature. The practice of taking large gruel meals is held to be responsible. According to Ogilvie the greater motility of the alimentary canal due to the more extensile mesentery is also a factor.

CARGINOMA OF THE STOMACH AND INTESTINAL TRACT

The rarity of malignant growths in the alimentary tract in native races has been the subject of much speculation. De Langen has laid special stress on the fact that gastric carcinoma is noticeably absent among the Javanese. The same is true in India and, as far as can be ascertained, in Central Africa. The comparatively short life-span of natives, in contrast to that of Europeans, may account for this difference.

CIRRHOSIS OF THE LIVER

All writers on tropical pathology have laid stress on the frequency of liver cirrhosis with ascites among native races, where the influence of alcohol can be discounted. Excluding cases caused by parasitic infection there remains a residue, of unknown ætiology, resembling the cirrhosis of Lænnec. Oudendal and other Dutch observers believe that the condition arises from chronic intoxication in a liver deprived of glycogen by undernourishment and starvation and there are now cogent reasons for believing that it is the result of chronic malnutrition which is accompanied by fatty infiltration of the liver and changes in the pancreas (Gillman and Davies, 1948) (see p. 447).

Snapper regards this as one of the commonest diseases of China and attributes it to intestinal intoxication in conjunction with deficiency of vitamins of the B complex. It is especially common in association with chronic bacillary dysentery and malnutrition. Megaw in India came to much the same conclusions (see p. 483). Hyperprotinæmia is invariable, and there is inversion of the albumin-globulin ratio. The scrum therefore gives a positive globulin test (see p. 158) and differential diagnosis has to be made from tuberculous peritonitis, adherent pericardium and kala-azar. A venous hum is audible between the xiphoid process and umbilicus.

Banti's syndrome with splenomegaly, anæmia, leucopenia and thrombocytopenia, with varying degrees of liver cirrhosis, is also met, especially in China.

Primary splenic abscess, which is very common in Rhodesia, was first described by Wallace at Broken Hill (Rhodesia) in 1922. He concluded that the abscess was caused by thrombosis of the splenic vein leading to a highly active necrosis of that organ when it had become secondarily infected. A tumour over the splenic area which is tympanitic is of itself suggestive. It is usually met in young adults. It starts abruptly with fever and pain in the left hypochondrium. This swelling rapidly enlarges upwards and downwards, thus raising the left dome of the diaphragm. When a splenic tumour is present a tympanitic note is very suspicious.

Diagnostic aspiration must be performed without delay. The aspirated pus is fluid, of a reddish colour, often frothy and sterile on culture.

DISEASES OF THE GALL-BLADDER

The rarity of cholecystitis in native races is striking. As the Editor has pointed out, there appears to be no direct connection between dysenteric infection and inflammation of the gall-bladder, nor is there any predisposition to cholelithiasis. De Langen and Lichtenstein report that among 150,000 out-patients in Batavia they were only able to make a diagnosis of gall-stones once, and among 422,943 other patients thirty times. Intrahepatic cholesterin stones, however, appear to be not infrequent.

DISEASES OF THE HEART AND BLOOD-VESSELS

Valvular heart disease in the tropics is usually syphilitic. Williams (1938) in Uganda found that syphilitic "heart is five times as frequent as any other cardiac condition; aortic syphilis (aortic regurgitation) was found in 86 out of 894 post-mortem examinations. The average age of onset of symptoms in natives is forty-one years, i.e., considerably earlier than in Europeans. Macfie and Ingram (1920) found cardiac aneurysm very frequent on the Gold Coast. Aneurysms, often multiple, are extremely common in the Chinese, and rupture is one of the most frequent causes of sudden death. In a series of 3,705 autopsies Davies in Uganda found cardiovascular conditions leading to congestive heart failure in 229.

Rheumatic valvular disease is a subject upon which much more precise information is required. W. T. James had never seen a case in twentyfour years' practice in Panama, and J. T. Clarke, in a series of 150,000 patients in Malaya, had the same experience. There is some evidence (see p. 19), that rheumatic infection does occur. Chesterman has seen typical rheumatic hearts at autopsy on the Congo. Barnes has found rheumatic carditis with valvular disease comparatively common in Fijians. Davies in Uganda, in a series of 2,994 autopsies reported evidence of rheumatic carditis only in 22 cases: mitral stenosis in 21, acute bacterial endocarditis, on the other hand, was present in 2.5 per cent. of all autopsies. Sclerosis of the coronary vessels appears in normal frequency with advancing age, as in Europeans, but it is a curious fact that the clinical syndrome of angina pectoris is usually absent. Formerly it was believed that arteriosclerosis was peculiar to the educated European classes, but recent researches indicate that, whenever the age is taken into consideration, there is practically no difference in vascular changes, which are at least as common in warmer countries as in the colder. Hyman (1946) found arteriosclerosis to be unduly common in Melanesians. Most were too old at fifty and many of thirty years had tortuous arteries. Blood-pressure readings as high as 230 systolic and 115 diastolic were recorded. Pulmonary and apical systolic murmurs are common in these peoples. Davies in Uganda has found that hypertensive renal disease accounted for 31 per cent. of all cardio-vascular conditions and was commonest between the ages of twenty and thirty. Hyperpiesia appears to be practically absent in poorer natives living on a carbohydrate dietary, though Wilkinson finds it common in South China, tending to increase with westernization of habits. It should be observed that the normal blood-pressure, systolic

and diastolic, in natives in the tropics, owing to smaller intake of protein, is 10-15 mm, of mercury lower than the normal in Europe. In those suffering from subnutrition, it is lower still. Under the heading of "endocardial fibrosis"—a form of heart disease which is peculiar to the tropics—has been discussed by Gray (1951). First described by Josserand and Gallavardin (1901), a series of 40 cases of unexplained heart failure in African troops was investigated by Bedford and Konstam in 1946. Davies has found it in 36 out of 3,759 necropsies in Uganda; Edge one in a European in W. Africa, and Gray two others in Europeans in Nigeria. Clinically this condition reveals itself as congestive heart failure of insidious onset in young adults. The main features are cardiac enlargement, low blood-pressure and sinus arrhythmia. Electrocardiogram shows low-voltage curves with inversion or flattening of the "T" wave. Embolic phenomena and opaque endocardium with fibrous tissue extending into the endocardial invocardium and mural thrombosis are almost always present. The apical portions of the ventricles are most commonly involved. Endocardial fibrosis is commonly associated with cosmonhilia.

The Editor who has seen two fatal cases in Europeans from Nigeria suggests an association with tropical cosmophilia. Gray believes that it belongs to an ill-defined category of collagen diseases and that A.C.T.H.

or cortisone should be tried out in these cases.

The juvenile form of thrombo-angiitis obliterans (Bürger's disease) appears to be common in native races and especially amongst the Southern Chinese.

Acute thrombophlebitis, originally described by Gelfand in Northern Rhodesia, assumed epidemic proportions in East Africa during 1943-44. Thrombophlebitis is accompanied by pyrexia of a relapsing character, sometimes associated with stiff neck. Three varieties of this syndrome have been described: (1) a short-term fever with stiff neck often followed by relapses, (2) thrombophlebitis affecting one or more limbs, (3) pyrexia without evident phlebitis. Most of the cases had been subjected to venipuncture and there is some evidence that the primary cause may be a virus possibly transmitted by syringes (C. Manson-Bahr and Charters). This suggestion has received some support from pathological studies which reveal proliferation of young capillaries and the presence of phloxophil intracytoplasmic inclusions. Gelfand (1947) has described symmetrical gangrene of the feet occurring in Africans from Mashonaland preceded by pain and cedema. It was seen only in males between twenty and thirty-five years. The gangrene occurred simultaneously on both sides. In four cases it was limited to the tips and pads of all the digits, but in one the whole of both feet up to 8 ins. above the ankle-joint was affected. There was no relation to malaria, syphilis, arteriosclerosis or ergot poisoning. In general this condition resembles the disease described by Lewis as due to damage to the internal coats of the digital arteries.

Gelfand now suggests that, in addition to affection of the vein, there is associated spasm of the corresponding artery and that this is the cause of cedema which is so striking a feature of this disease. It must be remembered that in pure venous thrombosis there is no cedema, no tender-

ness, little, if any, pain, but greater liability to embolism.

On the assumption of spasm planocaine may be injected into the lumbar sympathetic ganglia of the side corresponding to the inflamed vessels with the object of eliminating spasm. Gelfand now thinks that some of the cases of gangrene which have been described in Africans may indeed have been the result of arterial spasm.

DISEASES OF THE KIDNEY AND GENITO-URINARY TRACT

Vesical and renal calculi are amongst the most common conditions encountered in the tropics, the former being the more frequent, especially among boys and young men. Little is known of their exact causation. By some the explanation is thought to lie in the high concentration of the urine; by others in an unbalanced dietary with lack of vitamin A. Urinary calculi are specially common in South China. Where urinary schistosomiasis is common (Africa), the eggs of Schistosoma hæmatobium frequently form the nuclei of calculi.

Acute nephritis (acute glomerulonephritis) is commonly encountered, and is attributed to septic intoxication. De Langen and Wilkinson remark upon its frequency, especially in conjunction with scabies and with superadded septic infections. The clinical picture of contracted kidney with accompanying cardiac hypertrophy and hyperpiesia is rarely seen in indigenous natives, but in those who have adopted European habits, and in Chinese and Europeans in the tropics, it appears to be as common as elsewhere. The rarity of granular kidney is possibly correlated with the simpler diet and its low protein content. Chronic nephritis is especially common in South China.

The clinical picture of nephrosis (F. von Müller) is frequently seen. This is characterized by extensive and widespread ædema, and a high, but usually variable, albuminuria. There is a low total protein in the blood, and an inverted albumin-globulin ratio with increased cholesterolæmia. The urea and residual nitrogen are unchanged, whilst the blood-pressure remains normal without effect upon the heart. Nephrosis has often a syphilitic basis, and may be seen together with quartan and subtertian malaria (see p. 52). When all the causes are considered, there still remains a considerable proportion of cases without ascertainable ætiological basis, though many are found in association with ancylostomiasis.

Gonorrhæa, with its accompaniments, is one of the most common and widespread infections throughout the tropics. No one can estimate the extent of its prevalence or the disability that it causes. Not only is it responsible for joint and eye affections, but also for much serious disease of the female genitalia. Blacklock, in a thorough medical survey of Sierra Leone in 1930, estimates that 50 per cent. of males over fourteen have active signs and symptoms of this infection.

Epidemic epididymo-orchitis occurs in Malta and resembles the non-specific form described in England (Ainsworth-Davis). The fever which accompanies it occurs in two phases, a prodromal, followed by testicular fever, lasting four days. The testicular swelling subsides during the first week and resolves within a month. Atrophy occurs rarely.

DIABETES AND GLYCOSURIA

It has long been believed that true diabetes (diabetes mellitus) is very common in all parts of the tropics. This is possibly due to a high consumption of carbohydrates. The fact is that sugar (or substances which reduce Fehling's and Benedict's reagents) is comparatively often found in the urine amongst the Europeans and better-class natives in the tropics, but seldom in natives of the poorer class. De Langen, for instance, states that the incidence of diabetes in the Javanese is about 1 in 11,000, i.e., less than 0.01 per cent.

In India and Pakistan, diabetes is found among the richer people. Its comparative rarity in poorer natives is possibly to be ascribed to their shorter expectation of life. Diabetes usually develops in patients of riper years—those over lifty—and this factor may play a considerable part in statistical records. The relationship between obesity and diabetes is probably also important. Obesity is seldom seen in the average native, but among the rich, who can indulge more freely at table, a relatively higher incidence is observed.

The large number of cases of benign glycosuria in the tropics is remarkable, and these include the condition known as "renal diabetes." In this condition the blood-sugar content should not rise above normal. Patients with benign glycosuria feel perfectly well and show none of the usual symptoms of diabetes. The outlook in renal diabetes is favourable and the expectation of life is not affected.

GENERAL DISEASES

Gout.—It has always been held that there is a close connection between gout, obesity and overeating. It is also agreed that during the last half-century the incidence of this disease has almost everywhere decreased. It is always assumed that gout is very rare, or indeed non-existent, among tropical natives. Certainly it is soldom, if ever, observed in primitive peoples, and then only in those who have adopted European habits and customs. The Mahommedans suffer occasionally, while the Hindoos are said to escape entirely. In Manson's time gout was very rare in China, and in his diary he recorded one instance of gouty concretions in a Chinaman as an event of great importance. De Langen states that it has occasionally been observed in Java and the East Indies, but records in British India and in Central Africa are quite exceptional. Gout is said to be unknown in Egypt and in all the countries along the northern shores of Africa.

Endemic Fluorosis with characteristic mottled dental enamel and spondylitis occurs in its extreme form in some parts of India (Madras Presidency; Shortt and McRobert, 1987), and especially in Kweichow at the northern tip of Yunnan, China. It is due to drinking water containing fluorine.

Rickets—"Youbas" (Gold Coast).—Jelliffe (1951) has stated that, though rickets has been generally considered to be a rare disease in the tropics, it is found in West African children on the Gold Coast. This form is of a mild type and is ascribed to deficient maternal diet, to prematurity and insufficient exposure to ultra-violet light.

The dietary deficiency is due to prolonged breast feeding and weaning on a diet consisting mostly of carbohydrates with a complete lack of Vitamin D. The deficiency is accentuated by interference of calcium produced by phytic acid, which is present in maize (as in the maize paste known as "pap"). In children under two the anterior fontanelle is widely open with a soft spongy edge. There is gross caput quadratum and bossing of skull with classical "hot cross bun" (caput natiforme) appearance. In older children of eight to twelve the bosses are occipital and the X-ray appearances are likened to hair standing on end, or "needle forest spiculation."

Arthritis.—Arthritis, including the infective and rheumatoid forms, occurs in native races, but to nothing like the same extent as in Europeans in temperate climates. Exact figures are very difficult to procure, as it is necessarily very difficult to exclude gonorrheal arthritis. The available information has been included by McKinley in a table which purports to give the relative figures of incidence in various tropical and subtropical countries, but it is doubtful if the figures can be considered really reliable. In Ceylon, for instance, the number reported annually is given as 4,029, and the figure of 2,328 for the whole of India can hardly be considered accurate.

Dowling (1946) has described in Northern Australia a form of epidemic polyarthritis not reported elsewhere. It occurred in outbreaks of short, mild fever accompanied by polyarthritis, by pain and stiffness of several joints, especially those of hands and feet. Occasionally the knee joint is affected. The periarticular swellings persisted for 4–9 days. In the majority there was a papular or macular rash on the seventh day, occurring on the trunk and limbs and lasting 2–7 days.

Acute articular rheumatism.—This apparently exists all over the world, but infrequently in native races, especially where the climate is hot and dry; consequently, the incidence of rheumatic valvular disease of the heart is correspondingly rare. There are those who state that they have never seen rheumatic fever or endocarditis in a lifelong experience in India, Malaya and Central Africa. Thus, Mackinnon states that chorea is never seen in East African children. Fernando in Ceylon, however, from extensive clinical and pathological observations, found that rheumatic infection is an important cause of carditis and accounts for one-quarter of the total number of cardiac cases. Wilkinson has testified to its presence in South China. On the other hand, Chesterman on the Congo found it very rarely in the native population, but it has been recognized in African children on the Gold Coast and in Nigeria, where it occasionally leads to mitral stenosis. Although acute rheumatism has been noted with normal frequency in European residents it is difficult to obtain more accurate information from the meagre data available.

DISEASES OF THE RESPIRATORY SYSTEM

Tuberculosis.—It has gradually been recognized that the extent of tuberculosis in the tropics is much greater than was formerly thought possible. The rapidity of spread and malignancy of course of pulmonary tuberculosis when first introduced into the Pacific Islands have been

fully realized, and are well described by Robert Louis Stevenson among the Marquesans. Similar disasters have occurred in Fiji, Samoa, Tonga and other Pacific Islands. In India, Rogers (1919) found no less than 9 per cent. of deaths due to tuberculosis, and Megaw estimates that, in the whole country, two million people are suffering from it. Scott has drawn attention to the pathological peculiarities of tuberculosis in Southern China. It has proved to be one of the main causes of death in Jamaica, the Gold Coast, the Philippines, on the Congo, and in Tanganyika, where it has been studied by Wilcocks.

For the rapid spread of the disease, its virulent nature, and the poor resistance offered by primitive peoples, several factors are responsible. Usually the patients do not come for medical treatment until they are in an advanced stage. The sputum is loaded with bacilli and, living as they do in primitive huts or houses crowded together, infected natives are a constant source of danger to their fellows. Spitting is a universal habit, and undernutrition and co-existing malarial and parasitic infections render them all the more susceptible.

The most important factor in the epidemiology of tropical tuberculosis is contact. Natives are able to resist a first infection but, once the disease has become established, their resistance is low. During the last twelve years there has been an enormous increase in reported cases; in some instances, as in Nigeria and British Guiana, it has been five- and six-fold,

especially in the mining areas.

Unfortunately, tuberculosis is a disease which spreads with civilization, e.g., it was unknown many years ago in the Cameroons and in the southern Sudan. In Hong Kong, Scott, in an average of 4,000 autopsies a year, found marked tuberculosis in 5 per cent., and of these, three-fourths were children under ten. Tuberculosis among natives may be divided into two types, viz., "natural" tuberculosis, characteristic of those not immunized in any way against the disease, as in laboratory animals; and "modified" tuberculosis, a more chronic condition, so called because it is modified by primary infection.

It appears to be generally agreed that hæmoptysis is not a prominent sign of tuberculosis in native children, though extraordinarily frequent in adults. Scott has asserted that, however extensive the disease, however large the cavity, he has never seen fatal hæmorrhage in a child. Spontaneous pneumothorax is found, but amyloid disease in chronic cases is very rare. Bovine tuberculosis, though it occurs, does not appear to be common.

Intestinal tuberculosis and tuberculous peritonitis are especially prevalent in China, and bone tuberculosis in West Africa. Recent writers have all stressed the importance of the nutritional basis as a factor of the first

magnitude in the spread of tuberculosis in native populations.

Pneumonia.—Pneumonia, a principal cause of death almost everywhere in the tropics, especially in those countries with a persisting high humid atmosphere, has one of the highest mortality figures. Epidemics are specially found where native labourers are gathered together in compounds and in mining camps. The cause of the disease is usually a pneumococcal septicæmia, with little localization in the lungs. The clinical picture—rapid onset, extreme prostration and absence of the sthenic signs and

symptoms which characterize the disease in Europeans, and of a termination by crisis—differs very considerably from that seen in temperate zones. All these factors impart a varying clinical picture and confound the newly-arrived doctor in the tropics. The story of pneumonia and its ravages in the Rand Mines and in the copper belt of Northern Rhodesia is familiar to students of this subject. It is in the treatment of pneumonia in tropical natives that sulphonamides and penicillin appear to be having their greatest triumphs.

Syphilis of the lung is not uncommon in Bantus in South Africa. The lesions take the form of gummata or diffuse fibrosis. The signs and symptoms may resemble those of tuberculosis (Dormer and colleagues,

1945).

ZYMOTIC DISEASES

Scarlet fever (scarlatina).—All observers agree that scarlet fever either is never seen in the tropics, or is very rare. De Langen, in the Dutch East Indies, asserts that such cases as have been tentatively diagnosed eventually prove to be something else. Fischer and others who have looked for it amongst the negroes of Central Africa have never found it. Probably the disease exists on the Gold Coast and Nigeria in such a mild state as to be unrecognizable, and the rash may be almost invisible on a dark skin (Gillespie).

Application of the Dick test to a selected number of tribes in Tanganyika showed a certain percentage of positive reactions, equal only to about one-third of the figure usually observed in Europeans; the few cases reported from Central Africa have all been among European residents. Bötticher (1934) has compiled a review of this subject. In South America and the West Indies, on the other hand, the disease occurs in sporadic outbreaks. In India, too, it is known, though rare; it is of a mild type and specially apt to attack small children. According to Megaw and das Gupta, from 1923 to 1926 scarlet fever was reported from 212 districts, but nearly all cases were European residents. It is common in North China, though it does not occur in the south. Jensen (1940) states that in China and the Pacific Islands scarlet fever is newly imported, and that the nearer to the equator the less is the morbidity and mortality. Zöller (1925) found that the Dick test gave uniformly negative results.

Measles.—Measles is widespread throughout all tropical countries and runs the same course as elsewhere, and the malignant type is not uncommon. Where no inherent immunity towards the virus exists, as in the Pacific Islands (especially Fiji and Rotumah), a measles epidemic may cause a high mortality in adults as well as children; thus in 1874 over 25,000 Fijians died from this disease. The measles rash has to be distinguished from that of typhus and dengue, but its appearance, though

modified by a dark skin, is quite characteristic.

Diphtheria.—Diphtheria appears to be widespread and occurs in epidemic form, often when least expected. It is a disease of civilization and is evident only in towns and centres of population. It is recorded in the epidemiological statistics of most countries, with the exception of Africa. Whereas it is common in the northern and southern subtropical portions, it is apparently very rare in the tropical zone, and even at the

present day in East Africa, Uganda, Tanganyika and in West Africa, only

sporadic cases are discovered.

Mumps.—In the tropics this may be a generalized disease and assume a malignant form. In one-third of the cases orchitis is a complication. It is stated that the virus attacks the central nervous system, causing changes in the cerebrospinal fluid. Patients suffer from hallucinations and delirium—sometimes also they show Kernig's sign, bradycardia and ocular symptoms.

Bornholm disease, or epidemic pleurodynia, has been found in widespread epidemics in the Tonga and Cook Islands in the Pacific. The Europeans suffered equally with the native population (Matheson). An extensive outbreak has been reported by Jamieson and Prinsley from Aden in 1947. It is also known as the "devil's grip" or "epidemic myalgia." The virus (Coxsackie virus) occurs in the fæces and is diagnosed by the paralysis it produces in baby mice.

DISEASES OF THE CENTRAL NERVOUS SYSTEM

Syphilitic diseases of the central nervous system, such as tabes and general paresis, are seldom observed in Central Africa and the Pacific Islands, and this observation has been made the subject of much comment. In South China they constitute the commonest form of nervous disease.

Disseminated sclerosis is rare in most native races, and is not encountered

in the Chinese.

Epidemic encephalitis lethargica (Economo's disease) has been noted in

epidemics in Sarawak and in Cochin China (Bonnaire).

Epidemics of anterior poliomyelitis (infantile paralysis) occur in most tropical countries, notably in Malta, Singapore, St. Helena, Rhodesia, Kenya and Uganda, in spite of the apparent absence of this disease in the indigenous inhabitants, except for extensive outbreaks in the Belgian Congo and Mauritius.

Cerebrospinal meningitis occurs often in large epidemics, especially in the Southern Sudan, where sulphonamides have achieved remarkable

results.

Acute meningococcal septicæmia, a fulminating disease with petechial hæmorrhages in the skin and conjunctiva, without neck rigidity and with clear or faintly opalescent cerebrospinal fluid, is not uncommon in Africans. Sometimes the meningococci may be demonstrated in blood-films. According to Bell (1944) this serious form also yields to sulphonamide therapy.

GOITRE

Simple parenchymatous or colloid goitre is extremely common in Egypt, in the Nile Valley, Sierra Leone, in the Caji districts of the French Congo, and in the Ouelle and Katanga districts of the Belgian Congo. It has been reported in the Dutch East Indies, especially in the Island of Bali. In India it is most common in the Himalayan and Subhimalayan regions and in the parts drained by the great Indian rivers (McCarrison), as well as in the western provinces of China. Disorders of secretion resulting in exophthalmic goitre, myxcedema or cretinism are almost unknown.

It has been remarked that goitre is not found among the Bedouin or other desert tribes. In endemic goitrous districts iodine should be given to all girls between the ages of eleven and sixteen and to all pregnant women.

MALIGNANT GROWTHS

There is no truth in the oft-quoted popular statement that malignant growths are unknown, or are very infrequent, among primitive peoples. The truth probably is that, age for age, they are as frequent as in civilized communities. The absence of accurate vital statistics, age records, or even registrations of births and deaths, make such a comparison difficult. There are, however, certain special features of malignant disease amongst natives.

The outstanding facts about malignant growths in the tropics may be stated

categorically as follows:

- (1) The prevalence of primary liver carcinoma (12 per cent. of all carcinomata according to Vint), in 90 per cent. of cases grafted upon cirrhosis (Snijders). (Cazanove in French West Africa, Snijders and Straub in Sumatra, Strachan in South Africa, Smith and Elmes in East Africa, French observers in Dakar, Senegal.) In China (Snapper) primary carcinoma nearly always arises in a cirrhotic liver. Malignant changes in the bile ducts are far less frequent, but may be associated with Clonorchis sinensis infections (see p. 795).
- (2) The infrequency of gastric carcinoma.
- (3) The prevalence of malignant tumours on the sides of the neck.
- (4) The prevalence of skin carcinoma on legs and feet (grafted on chronic ulceration).

Many observers in recent years, especially Snijders, Straub and de Langen in the Dutch East Indies, Vint in East Africa and Rogers in India, have drawn attention to the fact that cancer should not be regarded as necessarily a scourge of civilization. Nor is it correct to state that the number of sufferers is increasing at a staggering rate. It was Hoffman, in compiling statistics for the United States Prudential Societies, who stated that the cancer rate was eight times as high amongst the 500 million of civilized races as among the 1,200 million uncivilized, including India; but Rogers's statistics, based upon 1,600 post-mortems in Calcutta, critically arrayed, showed no greater incidence of cancer in England than in India. The carcinomata were equally divided between the squamous and glandular epithelial forms, but the frequency of epitheliomata of the jaws in Calcutta is notable, and has also been recorded by French observers in Dakar, Senegal.

Malignant tumours, including both connective tissue and epithelial types, are about equally common in Bengal and in England, with a slight excess in the tropical country; but both innocent and malignant connective-tissue tumours are considerably more common in Bengal than in England. Vint has shown that, as far as Central Africa is concerned, there is close agreement between figures for malignant disease in natives, both in Nigeria and in Kenya. The large number of squamous-celled cancers in the latter country is due to malignant changes in chronic tropical ulcers of the legs, and to epitheliomata associated with this condition.

Carcinomata of the esophagus and nasopharynx are especially common among the Chinese.

A further peculiarity is the relatively high proportion of sarcomatous to carcinomatous growths. In the extensive series of 5,000 autopsies from the Dutch East Indies, malignant growths were found in 9 per cent., and the proportion of sarcomatous to cancerous tumours was 1:3.9, whereas in Europe

and America it is 1:10. Sarcomata of the very malignant round-celled type

greatly predominate.

Malignant disease of the breast is not uncommon in the East African native and, according to Vint, in almost 20 per cent. of cases it is found in males. Sequeira and Vint have pointed out that malignant melanoma, next to squamous celled cancer, is the commonest form of malignant disease in the natives of East and Central Africa, and O'Connor has stated that in Bengal malignant melanoma is distinctly commoner than in Europe. Most of the tumours are found on the foot, and the majority are on the plantar surface. Trauma is the most probable cause, as both sexes walk barefoot, and in a few instances "crab yaws" is an antecedent. The disease is usually locally malignant.

The clinical course of malignant growths differs, as a rule, between natives and Europeans. Through ignorance or fatalism, native patients resist to the very end before asking for medical aid, and are in a hopeless condition when

discovered.

There still remain certain other peculiarities, consequent on local habits and customs. Thus Spittel, Davidson and Turner have shown that cancer (epithelioma) of the cheek is the commonest malignant growth in Ceylon, and is as frequent in women as in men between the ages of thirty-five and fifty; here, no doubt, it is due to irritation caused by betel chewing. In Travancore, South India, it is also common, so that out of 1,700 cases collected by Bentall it formed 70 per cent.

Kangri-burn cancer is mainly found in Kashmir and is encountered in the older men. In the Mission Hospital there no less than 84 per cent. of the operations performed are for this condition. Kangri is an earthenware bowl 5–6 in. in diameter, surrounded by basket-work and surmounted by a wicker handle. It is heated by wood charcoal, and is worn against the skin under a loose garment. The growths are commonly found on the inner side of the thighs and anterior surface of the abdomen, above or below the umbilicus. The heat given out by the kangri is estimated at 150–200° F. The growths usually commence in the sears of previous burns. There are no metastases.

Burrows, Molesworth, and many other observers in Australia, have drawn attention to epitheliomata of the face, especially in Scottish and Irish immigrants, attributed to excessive irradiation by the ultra-violet rays of the sun.

CHAPTER III

THE TROPICAL ANÆMIAS

Macrocytic Anæmia of Pregnancy.—Synonym.—Tropical macro-

cytic anæmia.

Macrocytic anæmia has for some time past been recognized in India, Malaya, West Africa (Gold Coast, Russell) and other parts of the tropics, in pregnant women. In India it has been differentiated by Wills and others from the pernicious anæmia of pregnancy in temperate climates. The macrocytic anæmia of pregnancy comes on gradually during the second month, but the final breakdown may be sudden. As in pernicious anæmia, many of the clinical features are referable to decrease in the number of red blood-corpuscles. The tongue may be sore, but nerve changes are absent, and the oxyntic cells of the stomach secrete hydrochloric acid. Œdema of the feet and ankles is associated with low bloodpressure and pyrexia. Retinal hæmorrhages are common. This anæmia is essentially due to dietetic deficiencies, aggravated by superadded infections of malaria and ancylostomiasis; there appears, therefore, to be no essential difference between the macrocytic anæmia of pregnancy, as described by Wills and Mehta in India, and the nutritional macrocytic anæmia which has been made the subject of special studies in Macedonia by Fairley, Bromfield and Kondi. In macrocytic anæmia of pregnancy, many patients survive to term, but collapse during parturition. Premature labour is usual, unless the disease is treated in time, or, as on the Gold Coast, the child dies in the first few weeks of life. Anæmia associated with albuminuria suggests toxemia of pregnancy. If this condition is recognized in time and treated by blood transfusions and liver therapy, patients may proceed to term, but the children, though not themselves anæmic, are usually feeble. The response of this type of anæmia to liver therapy suggests that it is due to the lack of hæmopoietic principle. It is apt to recur in subsequent pregnancies.

Nutritional macrocytic anæmia.—This form is probably universal wherever the population is living on an unbalanced and deficient protein dietary. Nutritional anæmia is associated frequently with malaria, syphilis, and in India also with ancylostomiasis. Fairley, Bromfield and Kondi now recognize a macrocytic hæmolytic type, which is prevalent in Macedonia, and is accompanied by splenomegaly from chronic malaria infection. In this type there is primary nutritional deficiency with a hæmolytic agent—the malaria parasite—superadded. Males as well as females are affected. In addition to the anæmia there is a tendency to leucopenia with a shift to the left and a decrease in the platelet-count.

Trowell (1943) contends that it is better to think of the patient as having nutritional anæmia complicated by an infection of malaria or hookworm.

The anæmia is distinctly macrocytic. The average corpuscular diameter is about $8.6~\mu$. The red cells are, as in pernicious anæmia, more reduced than the hæmoglobin. There is much anisocytosis, but less polkilocytosis than in pernicious anæmia. Sternal puncture and the hæmocrit tube are

necessary for diagnosis. Trowell bases his classification on examination of the bone marrow as well as the blood examination and mean corpuscular hæmoglobin concentration. There is a mixed megaloblastic and normoblastic reaction in the marrow. Most cases show mixed deficiency of extrinsic factor and iron. Where megaloblasts are found in the marrow, liver extracts are needed for treatment.

In Fiji macrocytic anæmia is found solely amongst Indians resident there and the greatest incidence is in these women during the last months of pregnancy and during the purperium. This severe anæmia is frequently associated with high fever which responds to the treatment of the anæmia. There is normal acidity of the gastric juice. The mean corpuscular volume is between 100 and 123; the mean corpuscular hæmoglobin concentration



Fig. 1.—Sickle cells. Fresh blood preparation after forty-eight hours. (Bulletin of the Johns Hopkins Hospital.)

between 26–37 per cent. and colour index varies between 0.9–1.5. A definite seasonal incidence has been observed with a peak in the latter half of the year. The cases can be classified into those responding to Vitamin B_{12} (Cytamen) and those responding to folic acid. In the former group there is also an associated iron deficiency (Clinton Manson-Bahr).

Treatment.—This anemia responds quickly to liver or liver extracts. Crude extracts are most effective; larger doses are required than in pernicious anemia. It is said that anahemin is not effective. Foy, Kondi and colleagues (1952) have found that the megaloblastic anemias of Africans respond in a most remarkable way to intramuscular injections of crystalline penicillin G, 400,000 units daily.

Differential diagnosis.—In pernicious anæmia there is achlorhydria and a positive van den Bergh reaction, whilst in tropical nutritional anæmia

the opposite obtains. Glossitis is said to be much commoner than in pernicious anæmia. Tropical nutritional anæmia has also to be distin-

guished from the macrocytic anæmia of sprue.

Erythroblastic anæmia of childhood (thalassæmia, Cooley's anæmia) is peculiar to the Mediterranean area, especially to Cyprus, and is a chronic, ultimately fatal, anæmia of early onset in children of Mediterranean stock, of Mendelian dominance, with splenomegaly, peculiar bone changes, most conspicuous in the skull, familial incidence, presence of large numbers of normoblasts in the peripheral blood and a mongoloid facies. Some of these features may be absent. The preponderance of the disease is in males. Sometimes there is a febrile onset and a history of geophagy. The radiographic bone changes are characteristic, with thickening and distinctive striation of the calvarium. There is a continuous gradation of all degrees of severity. The anæmia is hyperchromic and in some there is a small proportion of more primitive cells than normoblasts known as "target cells." These are erythrocytes with a lightly stained zone between the deeply-stained centre and the periphery. In bone marrow films there is an enormous proportion of normoblasts. The interval between birth and onset renders it unlikely that there is much in common between this and erythroblastosis fætalis. Wintrobe has described as "target cell anæmia" an adult form of Cooley's anæmia in which bone changes are usually present and the erythrocytes show an increased resistance to hypotonic saline solutions. The harbouring of this trait is of no consequence to the individual "carrier" though it may be transmitted to the offspring. There is no therapy beyond repeated blood transfusions.

Sickle-cell anæmia—sicklæmia.—Sickle-cell disease, or "sickle-cell trait," is a severe hæmolytic anæmia in which the red cells assume a peculiar sickle shape after withdrawal from the body (Fig. 1). It occurs mostly among negroes, though sometimes found in mulattos. Lehmann and Cutbush have found it in aboriginal races in India, especially the "Veddahs," and Wallace and Killingsworth in Mexicans, and in wild deer in America. It is characterized by remissions and exacerbations of the anæmia, associated with joint pains and a tendency to ulceration of the legs in 40 per cent. First described by Herrick in 1910, it formed the basis of a fine study by Huck (1923). Nearly all the cases have been described in the United States and West Africa, where it occurs in 12.4 per cent. of the population, irrespective of tribe or locality (Findlay and Robertson), though no Europeans have been found affected there. On the whole, it is a fairly rare disease, and the sickle-cell trait is present in 5-7 per cent. of all American negroes, quite irrespective of health. In the Yorubas of West Nigeria it is present in 23.7 per cent.

This disease probably originated in Africa, whence it was imported into the United States; and recently the sickle-cell trait has been found by Evans in 20 per cent. of bloods in the Gambia. It is a hereditary and familial disease with a Mendelian dominance, and is transmitted equally by male or female. Cooley and Lee have drawn attention to the probable tribal origin. The sickle-cell trait is not invariably associated with

 $^{^1}$ The sickle-cell trait has been found in Greece by Chovemis et al. in 1951.

anæmia. Pauling demonstrated that sickle-cell phenomena are associated with the globin portion of hæmoglobin. As the trait is a heterozygous condition (Ss), or a homozygous state (SS), then sickle-cell anæmia can only arise as the result of mating of two heterozygous individuals (Ss \times Ss) or mating of a heterozygous and a homozygous (Ss \times SS) or two homozygous (SS \times SS).

Dilated and tortuous retinal vessels are usually observed and microaneurisms of the retinal arteries have been demonstrated (Harden, 1937, Ray and Cecil, 1944). Sickle-cell anamia crises may occur in pregnancy with fatal results.

Sickle-cell anemia has to be distinguished from ovalocytosis, which is a hereditary familial condition, in which the elliptical shape of the red cells (like that in camel's blood) is transmitted in a Mendelian manner. The young red cells in the bone-marrow have the normal round shape, and assume an oval form when they become mature.

Sickle-cell disease begins in childhood, and males are affected three times as frequently as females. Symptoms may appear even at seventyeight years of age though, according to Robertson and Findlay (1947), the average age, at the time of the hæmolytic crisis, is 25 years, and sufferers from sickle-cell anemia rarely survive beyond the third decade. The red cells are larger than normal, and show either a normal or decreased fragility. Target cells are commonly present. The sickling develops usually only after the blood has been withdrawn and ordinary stained blood films reveal the sickle shape only in very severe cases. Incubation with bacterial suspensions or trypanosomes produce the same effect with greater rapidity. Scriver and Waugh (1930) showed that local moist stasis, produced by a rubber band round the finger, very materially increases the proportion of sickle cells. This is considered to be the most reliable and practical method (Diggs and Peltit, 1940). The wet-blood films should be ringed with vaseline and allowed to stand over-night. Findlay recommends that blood should be taken from a vein under paraffin and fixed directly in formol-saline under a liquid paraffin seal. Cooley and Lee have shown (1926) that in preparations kept in the incubator the sickle cells disappear, leaving the normal round cells intact.1 Fatal hæmolytic crises, with intense jaundice, may supervene, especially in pregnant women. Then there is bilirubinæmia and hæmoglobinæmia, sometimes with hæmoglobinuria, together with severe joint pains, and others in abdomen and chest simulating coronary thrombosis. Infarction lesions in the femora have been demonstrated (Edington).

The latent phase of the disease is much commoner than the active one; in that only a few sickles can be found in perfectly fresh blood, but large endothelial cells may be seen engulfing red corpuscles. Nucleated red cells are always present (Cook and Meyer, 1915). In severe cases the red cells are reduced to 2–8 million, and the leucocytes increased to 15,000 per c.mm. Basophilic stippling of the red cells is common and the blood platelets are not diminished (Mason, 1922). No difference in crystal structure can be detected in normal or sickle-cell hæmoglobin. Blood

 $^{^{1\,\}prime\prime}$ False " sickling takes place from changes in the plasma brought about by prolonged incubation (Isaacs, 1950).

transfusions are the only sure method of saving life during a hæmolytic crisis.

Pathology.—The bone-marrow is hyperplastic and contains sickle cells. The spleen may be enlarged or may be atrophic and fibrotic. Rich has described characteristic lesions in the spleen: there is a congenital malformation of the sinuses, which permits free escape of blood into the pulp, and this is especially marked round the Malpighian bodies. Osteoporosis of the bones is common. The sickle character can only be recognized in formalin-fixed sections. Graham (1924) has made a minute pathological study of this disease and finds chronic hepatitis and cholelithiasis common.

Symptoms.—Jelliffe now recognizes the following clinical types:-

- (1) Sicklæmia (symptomless carriers of sickle-cell trait; meniscocytosis or depanocytosis).
- (2) Sicklæmia with thrombosis.
- (3) Latent sickle-cell anæmia.

(4) Sickle-cell anæmia (Meniscocytic anaemia; depanocytic anæmia; African anæmia).

Sickle-cell anæmia may remain latent throughout life. On the other hand, there may be an active phase causing severe chronic anæmia of the hæmolytic type, associated with weakness, dyspnæa, a tendency to ulceration of the legs resembling indurated syphilitic ulcers (Huck), a yellowish discoloration of the scleræ, and jaundice, especially when blood destruction is very great. The liver and spleen are usually enlarged. There may be thrombi in the small vessels of the lungs, giving rise to symptoms of cardiac disease. There is usually a positive indirect van den Bergh reaction.

When the disease is active there may be intermittent paroxysms of fever, associated with severe joint pains which may last two or three weeks. Patients with this anæmia usually do not live beyond middle age, and death takes place from intercurrent infections. Cerebral necrosis, and thrombosis with paresis, have been recorded. The latent disease may be stimulated into activity by any infection. Hæmoglobinuria has been reported and in Africans it is most difficult to differentiate from blackwater fever. In Nigerian children Jelliffe has described bossing with "needle forest" appearance of the skull. There is also hepatomegaly with well-markéd clubbing of fingers and toes. Liver puncture tests show definite derangement of hepatic function.

Blood changes.—Sometimes the blood is macrocytic, and there is a neutrophil leucocytosis of 10,000-30,000. Polychromasia is marked; there is a reticulocytosis of 25 per cent. and normoblasts are common.

If citrated blood is kept under oil for twenty-four hours, and formalin then added, the test for sickle cells becomes more delicate.

Treatment.—The treatment is purely symptomatic. The anæmia may be improved by iron and liver therapy. Blood transfusion is of distinct value in relieving paroxysms of blood destruction. Splenectomy has been employed with some benefit in selected cases, but the sickling is unaltered by this operation, which renders the patient more susceptible to subsequent subtertian malaria.

Baghdad spring anæmia.—A new form of acute anæmia is reported in Baghdad, appearing only for a few weeks in spring. This anamia, according to Lederer, runs a very rapid course, and a severe degree is produced within 24 to 36 hours. The mortality is about 10 per cent. It is curable by blood transfusion, liver therapy in massive doses and injection of adrenalin. The disease is confined to boys, for the main part Jews, especially those of a certain constitutional type. It is suggested that the hæmolysis is due to anaphylaxis by contact with flowers (Verbena hybrida) and young fruits. The administration of blood has a double effect, counteracting shock as well as stimulating the bone marrow. In mild cases whole blood injections (10-20 ml. intramuscularly) suffice; but in

severe degrees intravenous transfusions are necessary.

Chlorosis.—This has almost disappeared from Europe, but is probably related to the hypochromic, microcytic dietetic anamias (chlorosis tarda) of the tropics, which are such a frequent accompaniment of subnutrition and are due to lack of iron intake and absorption. This condition is seen especially in young native girls in the first year after the katamenia. anæmia gives the face a peculiar dull green colour which is masked by the pigmentation of the skin. Some of these cases have spoon-shaped nails (koilonychia) with stomatitis and dysphagia—the so-called Plummer-Vinson syndrome (see p. 439). Investigations of anæmia in Indian soldiers in the India-Burma campaign, 1948, showed that iron-deficient anæmia formed a major problem. The main cause of this anæmia was found to be the low iron reserve which could not be sufficiently supplemented by the Army diet.

Lymphatic leukæmia and spleno-medullary leucocythæmia appear to be

met as frequently as in Europe.

The position of pernicious (Addisonian) anamia is by no means so well It appears to be a disease of northern peoples and is either rare or unknown in the tropics and subtropics. Wilkinson states that it does not occur in South China. De Langen and Lichtenstein assert that they have never seen it in the course of their extensive studies in Java; it is said to be very rare in Ceylon and in South Japan. In Central Africa no cases are found in negroes. A diagnosis of pernicious anæmia should not be established without proof of achylia gastrica and megalocytosis, the latter ascertained by sternal puncture.

Thrombocytopenia vera is not uncommon in South China, and is undoubtedly to be found in many native races (see Onyalai, p. 699).

Section I.—FEVERS

Subsection A.—FEVERS CAUSED BY BLOOD PROTOZOA

CHAPTER IV

MALARIA

Definition.—The term malaria includes all fevers produced by endocorpuscular parasites of the genus Plasmodium which give rise to periodic fevers accompanied by anæmia, enlargement of the spleen and deposit of black pigment in the internal organs. Somewhat similar parasites occur in birds, bats and monkeys. Malaria heads the list as the most formidable of tropical diseases, and in India it is estimated to be responsible for at least two million deaths a year.

Geographical distribution.—Benian tertian malaria in Europe extends to 65° N. (Lake Ladoga, Archangel and S. Sweden). It is still to be found in Denmark, Holland and Emden district of Germany; was until recently endemic in S.E. England and the carrier Anopheles atroparvus. In America it extends to 40° N. in Sacramento Valley and in Canada to 44° N. on L. Ontario. In the southern hemisphere it extends to 20° S. in Queensland, 30° S. in Natal, and 40° S. in S. Argentine. Malaria is rare above 6,000 ft. but is found in Quito (8,500 ft.), Addis Ababa (8,400 ft.) and in Londiani, Kenya (7,800 ft.). Uncommon in W. Africa it was introduced in the middle of last century to Mauritius and Réunion.

Barbados is free from malaria (though a small epidemic broke out in 1927) and so are the islands of the Pacific, E. of 170° E.

Ovale tertian malaria, identified in 1922, is a particularly mild form of fever with tertian periodicity appears to occur for the most part in Central Africa, and is found in Sierra Leone, the Gold Coast, Nigeria and Uganda. A few infections have been reported from Turkmenistan,

Palestine, Egypt, Mauritius, Venezuela, India and the Philippines.

Quartan malaria until comparatively recently appears to have been commoner in temperate latitudes than in the tropics. It is recorded from Central Europe, sparingly in the Mediterranean area—in Italy, Macedonia, Palestine—Iraq, South India and the Andaman Islands. and is the dominant form in South Ceylon (except in epidemic outbreaks), in parts of Malaya, in New Guinea and adjacent islands. In Africa it is found sparingly, especially in the central portion. In America it is uncommon in the West Indies, but common in Antigua, Panama and Brazil. In Macedonia and the Caspian area the maximum incidence is from July to November, and in many localities it appears to be confined solely to children (from 2-10 years) as, for instance, in Salonika and the Western Solomon Islands.

Subtertian malaria is much more "tropical" in its distribution. It is limited by the mean summer temperature of 70° F. (21° C.) and a mean winter isotherm of 48° F. (5° C.). In Europe it is rare, except in the Balkans

and the Danubian marshes, but in the tropics it is the prevalent form. wherever fever is specially virulent. In 1920 subtertian malaria was imported into Central Russia by refugees from Turkmenistan and spread as far north as Moscow where cases occurred even during the winter season. It is found in desert oases, especially in Somaliland where its occurs in great epidemics after the rains. The vector A. gambice disappears in the dry season when larve are found in the deep wells (M.T. Gillies). is the chief form found in almost the whole of West and Central Africa. Asia Minor and in parts of Malaya and Central India. In the American continent it was formerly abundant in Panama and constitutes a menace in North and Central Brazil. Although this form is usually not met at high altitudes, Garnham has recorded sovere epidemics at Londiani, Kenya, at 7,800 ft. on farms where African squatters live. From February to May the mean temperature is 61° F. and A. gambiæ the vector—a species which in that area spends most of its life in human habitations where the temperature is 5-10° F. higher than outside. that situation the mean temperature is 66° F., which suffices for the sporogony of P. falciparum. Heisch and Harper have described an epidemic of malaria in Kericho, in the Kenya highlands, where the vector is A. funestus.

Epidemiology and endemiology.—Conditions which favour the presence and breeding of anopheles mosquitoes tend to the increase of malaria, and *vice versa*, and whatever favours access of these insects and the parasites they contain also favours the acquisition of malaria.

Malaria is a disease of the open country and villages rather than of towns. These circumstances are related to the distribution of anopheline mosquitoes which occasionally, under favourable conditions, increase and spread. New species may be introduced into an area, as has happened many times in the world's history. The latest example was the introduction of A. gambiæ in 1930 into Natal, Brazil. This resulted in the greatest epidemic ever recorded in that country. There were at least 100,000 cases and 14,000 deaths. This, despite the fact that malaria is endemic in Brazil.

In subtropical regions subtertian malaria is a primary infection in summer and early autumn, hence the popular term—æstivo-autumnal fever. This peculiarity can be explained to some extent by the higher atmospheric temperature required for its development in the mosquito. Hence, though benign and subtertian forms are frequently associated, and the latter can be acquired at any time in the tropics, it is only in the summer and early autumn that subtertian can be acquired in more temperate zones. When the temperature falls below 15° C. development of the oöcyst in the mosquito is arrested, but when once the sporozoites have entered the salivary glands, they are capable of infecting man, even during the winter season. There is no evidence that any particular type of malaria is associated with any particular species of anopheles. Generally speaking, the most important conditions necessary for the propagation of the benign tertian parasite are the sustained average temperature of at least 60° F. (15.5° C.) and a humidity of at least 63 per cent.

There are other factors to be considered. Wenyon explained the seasonal variations of the two dominant forms of malaria in Macedonia.

and Palestine by the fact that the benign tertian tends to relapse over a longer period and is more resistant to quinine, whilst the subtertian is more amenable to treatment and there is less tendency for infections to persist from one season to the next. Though the numbers of benign tertian and subtertian cases may be approximately equal in the height of the season, subtertian malaria more rapidly develops a heavy infection and produces a greater number of gametocytes; thus, it tends to spread in epidemic form with greater rapidity. The spread of malaria is also intimately related to the susceptibility of the human host.

Immunity produced by previous infection is another consideration (see p. 74). D. B. Wilson states that subtertian malaria causes little illness in the adult Bantus of parts of Tanganyika, though all babies are infected in their first few months of life, and suffer severely before im-

munity is acquired.

As a rule, malarial infection declares itself a week or ten days after the infective bite of a mosquito. In some individuals the incubation period may be greatly prolonged; the benign tertian malaria in Holland, for instance, is thought to be due to infection acquired during the preceding autumn. Doleman in Middelburg, Zeeland, considers the healthy carrier an important factor in this respect producing relapses in April and May of the following year. Full infection takes place in July and August reaching its peak in the autumn months. Swellengrebel, on the other hand, believes that from June to August, A. atroparvus mosquitoes fly in and out of houses to lay eggs and so any infections acquired are injected into domestic animals, but in September egg-laying ceases, but atroparvus continues to feed on blood and they remain in the houses. Therefore the infections they then acquire are passed to man only.

Malaria incidence is usually endemic, but hyperendemicity is a distinct form, demanding for its production such an intensity of transmission that a high degree of tolerance to the effects of reinfection is induced in those who experience its effects over a number of years. This tolerance is accompanied by a capacity to contend effectively with the parasites of the locality. The frequency of transmission that is necessary to induce this state is certainly not less than 30 times a year. In the presence of this intensity of infection newcomers, usually infants, suffer severe attacks of malaria and a proportion, between 10 and 20 per thousand of the infant population, die annually in the absence of treatment. After 18 months they are out of danger, and from then on and throughout life there is no increase in the parasite load, as a result of seasonal heightened intensity of transmission.

The World Health Organization has proposed the following classification:—

- I Hypoendemic Malaria with spleen rate in children 2-10 years of age 0-10 per cent.
- II Mesoendemic Malaria with spleen rate in children 2-10 years of age 11-50 per cent.
- III Hyperendemic Malaria with spleen rate in children 2–10 years of age constantly over 75 per cent. Spleen rate in adults high.

IV Holoendemic Malaria with spleen rate in children 2-10 years of age constantly over 75 per cent. Spleen rate in adults low; it is in this type of endemicity that the strongest adult tolerance is found.

ÆTIOLOGY OF MALARIA (PLATE II)

The four species of parasite (*Plasmodium*) causing malaria in man differ from each other in morphology, but the general course of their life-history is similar. They all have two distinct phases: intracorporeal and extracorporeal. Each species has its special intracorporeal erythrocytic life-cycle that may last approximately 48 to 72 hours. It was estimated by Ross that at least 150 million malaria parasites must be present in the peripheral blood before an attack of fever is produced. The extracorporeal stage is undergone in the body cavity of an anopheles mosquito.

The malarial parasite can be recognized in fresh unstained malarial blood an hour or so before a paroxysm; it is a pale disc inside the red

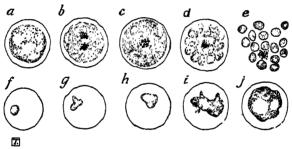


Fig. 2.—Evolution of the tertian parasite, unstained.

blood corpuscle (Fig. 2, a), and at a later stage a number of fine black or reddish-black particles of pigment (hæmozoin, formerly known as melanin) are scattered throughout its protoplasm. This pigment is believed to be the excrement of the parasite. It collects, as the parasite grows, in central blocks round which the protoplasm becomes divided into segments (merozoites); when the cycle is complete the containing corpuscle (host cell) breaks down and liberates the merozoites, none of which contain hæmozoin. This stage coincides with a clinical fever.

A number of these freed merozoites escape phagocytosis by wandering leucocytes and attach themselves to other red corpuscles, enter them, and grow at the expense of the hæmoglobin, exhibiting active amœboid movements. When appropriately stained, the free merozoites are seen to consist of a nucleus surrounded by a ring of protoplasm; as they reach maturity a nucleolus becomes visible (Fig. 3, α , j). In the pre-sporulation phase the nuclear elements become scattered throughout the protoplasm, and around them the segmenting parasite arranges itself to form merozoites (Fig. 3, b, c). The vesicular character of the nucleus does not become apparent in the merozoites until they lie free in the plasma. The hæmozoin or pigment particles of the malaria parasite are either black or dark brown dust-like specks, grains or rods, isolated or aggregated into

PLATE II

MALARIA PARASITES. × 2.000

A.—SUBTERTIAN PARASITE (Plasmodium falciparum).

- Fig. 1.—Subtertian rings. Note the marginal form and, in one, double chromatin dots.
- Fig. 2.—Quarter-grown parasite. When seen in the peripheral blood this denotes a severe infection, as it normally occurs in the capillaries of the internal organs. Note discolouration of cell, its irregularity and the pernicious stippling—known also as "Stephens's" and "Christopher's" dots, also as "Maurer's dots" or clefts.
- Fig. 3.—Schizogonic stage, or rosette form, with thirty spores, also usually in capillaries of internal organs—seldom seen in peripheral blood.
- Fig. 4.—Male gametocyte (crescent).
- Fig. 5.—Female gametocyte (crescent) showing concentration of chromatin and pigment.

B.—BENIGN TERTIAN PARASITE (Plasmodium vivax).

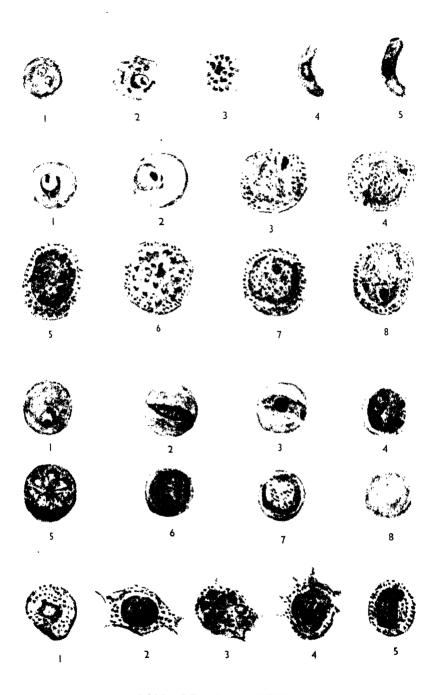
- Fig. 1.—Young ring form.
- Fig. 2.—Quarter-grown parasite. Note Schüffner's dots and slight enlargement of corpuscle.
- Fig. 3.—Half-grown parasite. (Amœboid form).
- Fig. 4.—Three-quarter parasite. (Amœboid form).
- Fig. 5.—Presporulating stage showing fragmentation of chromatin.
- Fig. 6.—Complete schizogony. (Rosette stage with 20-24 spores).
- Fig. 7.—Male gametocyte. Note loose arrangement of chromatin and purple tinge of protoplasm. The pigment is coarser and blacker than in the female.
- Fig. 8.—Female gametocyte. Note compactness of chromatin and blue tinge of protoplasm.

C .- QUARTAN PARASITE (Plasmodium malariæ).

- Fig. 1.—Ring form,
- Fig. 2.—Quarter-grown parasite ("band form"). Note corpuscle is not enlarged.
- Fig. 3.—Half-grown parasite ("band form"). Note the scattered dark pigment.
- Fig. 4.—Presporulating stage.
- Fig. 5.—Complete schizogony. (Rosette stage with 8 spores).
- Fig. 6.—Male gametocyte. Note purple tinge of protoplasm with heavy pigmentation, coarser and blacker than in the female.
- Fig. 7.—Female gametocyte. Note blue tinge of protoplasm. (Stipplings, when present in the blood corpuscle, are known as Ziemann's dots.)
- Fig. 8.—Normal red blood-corpuscle for comparison of size.

D.—OVALE TERTIAN PARASITE (Plasmodium ovale). (After James, Nicol & Shute.)

- Fig. 1.—Ring form. Note Schüffner's dots.
- Fig. 2.—Presporulating stage. Note irregular and oval shape of corpuscle with coarse and prominent Schüffner's dots.
- Fig. 3.—Complete schizogony. Note irregular distribution and oval shape of spores, and also distortion of corpuscle.
- Fig. 4.—Male gametocyte. Note coarse Schüffner's dots and purple tinge of protoplasm.
- Fig. 5.—Female gametocyte. Note marginal arrangement of pigment.



MALARIA PARASITES

PLATE II

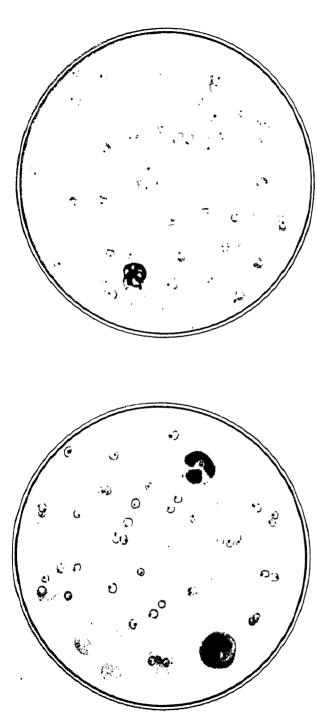


Fig. 1.—Blood-film from fatal case of subtertian malaria, showing heavy '' ring '' infection. (Giemsa's stain).

Fig. 2.—Thick blood-film preparation of subtertian rings and crescent stained by Leishman to show appearances after dehæmoglobinization. x 1,000. (From a preparation by Dr. H. Seidelm).

THE BLOOD PICTURE IN SUBTERTIAN MALARIA

PLATE III

more or less dense clumps. As long as the nucleus remains entire, the hæmozoin is peripheral, but when segmentation takes place it becomes central.

The extracorporeal or mosquito stage commences with a process of exflagellation. This is a sexual phase which can take place in the blood

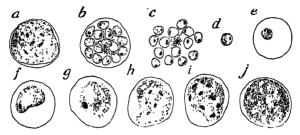


Fig. 3.—Evolution of the tertian parasite, stained.

after it has been withdrawn from the body. As observed in fresh wet preparations of blood the flagellated body is derived from the male sexual cells or gametocytes, which are composed of protoplasm and hæmozoin and which possess, on more minute examination, a distinctive structure. These sexual cells are usually round, but in subtertian malaria (P. falciparum) they are crescentic. These well-known "crescents" become rounded off before flagellation. The flagella (more correctly, the microgametes) number from one to six or more. They are extremely delicate filaments, which move about rapidly and which every now and

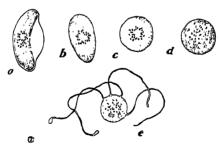


Fig. 4.—Evolution of the flagellated body from the crescent (male gametocyte).

again break away and swim about with vibratile movement. Only the male cell (microgametocyte) undergoes this process; the female (macrogametocyte) remains rounded and stationary until fertilized by one of the erupted flagella (microgametes). This event signalizes the first stage in the development of the malaria parasite in the stomach cavity of the anopheles mosquito. There sporozoites develop in the oöcyst on the stomach of the mosquito and later migrate to the salivary glands of this insect, gaining entrance to the blood-stream of man via the saliva. They then penetrate the hepatic cells where the pre-erythrocytic and exocrythrocytic cycles take place for seven days or longer.

A latent phase of the malaria parasite in the human body.—
It is a well-established fact that when the fever subsides the parasite disappears from the general circulation, either spontaneously, or as the result of the administration of anti-malarial drugs. After an interval of weeks or months, however, the parasite may reappear in the peripheral blood. In benigh tertian and quartan malaria it may be as long as nine months or a year after quinine, atebrin or plasmoquine treatment (see p. 87). Jordan has recorded one case in which the primary clinical attack was delayed for 27 months.

The relapse cycle of the malaria parasite has now been proved to take place in the hepatic cells (in *P. vivax* and in *P. falciparum* of man). The primary protozoal mass in the liver is known as a *cryptoschizont*, which divides later into *cryptomerozoites*. There are thus four distinct cycles of development—the *pre-crythrocytic*, the *exo-crythrocytic* in the liver cells, the *crythrocytic* in the red blood corpuseles, and the *sexual* commencing with the growth of gametocytes in the blood and continuing with *sporogony* in the tissues of the mosquito. (For full details *see* p. 900.)

The metabolism of malaria parasites.—Speck and his colleagues (1946) have found that acid products are formed from carbohydrates by malaria parasites; thus cell-free extracts of P. gallinaceum cause glycolysis by reactions similar to those occurring in yeast or muscle in which glucose is oxidized through pyruvate as an intermediate. Pyruvate oxidization takes place in parasitized cells as well as in the free state, through the well-known tricarboxylic acid cycle of Klebs. The former oxidize glucose, lactate, pyruvate, succinate and malate rapidly, whilst lactic acid is formed by free parasites from glucose and markedly reduces oxygen consumption. It has been shown that malaria parasites may suffer from lack of vitamins in the diet quite as much as the host does and that P. gallinaceum requires pantothenic acid and "biotin" just as much as streptococci do and, if chicks are subjected to a severe deficiency of this vitamin, the malaria parasites cannot grow in the red blood corpuscles and only very mild infections result, but the cryptozoite generation is not handicapped in this way. The results of pantothenate deficiency can be produced by the administration of "homologue blockers" such as pantoyltauramido-4chlorobenzene.

Suppression of malaria by milk.—In connection with the nutritional needs of the malaria parasites, Maegraith and colleagues (1953) have made the somewhat remarkable discovery that a diet of milk and vitamins renders rats resistant to malaria parasites (P. berghei). This may link up with the work of György who has found that milk increases the resistance to infection by certain bacteria, and a further possible link is the fact that human infants in the first 3–4 months of life seldom suffer from malarial infection. It is possible that insufficiency of biotin is a possible explanation as milk contains little of it.¹

Transmission of malaria by blood transfusion, drug addiction and salvarsan injections.—There is risk of conveying malaria in the

¹ Hawking has found that P.A.B. (*P-aminobenzoic acid*), absent from milk, is necessary for the growth of the parasites and their development is prevented by antagonist substances, such as prognanil and pyrimethane.

TABULAR STATEMENT OF THE CHARACTERS OF THE FOUR SPECIES OF MALARIA PARASITE

Relative number of parasites in peripheral and Liability to relapse visceral blood	d Parasites numer- Relapses noted in out in all parts up to 3 years of the body in from time of various stages original infection.	As in P. vivax.		The chief de- velopment of the parasite takes place in the in- fernal organs; hence the rela- tice scarcity of all, save most immature forms, im peripheral
Form of Alterations in corpuscles	Round or Hypertrophied slightly ovoid and pale; stiplarger than pled with Schiff-the red cell.	Slightly oval, may be slightly		
Number of Femore of gan	14-24 Rou average slig! large	6-12, Rou average sligh size	тээ	8-32, sometrin es tin es more, able.
Adult	Larger than a red cell.	Slightly smaller than a		н
Trophozoites	Signet rings of various sizes; growing forms irregular in size, with vacuole.	Signet rings, as in P. wivax; growing forms band-	Vacuole soon disappears.	., ., ., ., ., ., ., ., ., ., ., ., ., .
Hæmozoin	Fine, yellowish brown.	Coarse, and dark brown.		Figment blacker than in other forms; may be aggreeined coarse gatedinto coarse granules.
Move- ment	Active amœ- boid.	Slight, in im- mature forms.		Active amæ- boid.
Duration of schizogonic cycle	48 hours	72 hours		24-46 bours (irregular)
	1. Benign tertian parasite, Plasmo- dium vivar.	2. Quartan parasite, Plasmo-dium		S. Subter- tian parasite, Plarasite, Atuano, Atuan fal- ciporum ciporum and malaria).

transfusion of citrated or stored blood; *P. vivax* especially may be found in the blood of donors exposed to infection within four years before the transfusion. A summary of recorded cases has been given by McClure and Lam (1945). In London a case of fatal quartan malaria has been recorded in a baby transfused with compatible blood from its father who had lived in Ceylon twelve years previously and who had never suffered from any clinical manifestations of malaria (Nabarro and Edward). Gardner and Dexter have recorded a similar instance in which the interval was seventeen years. There have been several instances of transmission of quartan with blood refrigerated for four days (Rogers, 1947). Boventer has found *P. vivax* viable for 13 and *P. falciparum* for 21 days.

In non-malarial countries persons who have had malaria should not be used as blood donors. In malarial countries this rule cannot apply. If fresh blood must be used, the recipient should be given quinine, paludrine or atebrin as a prophylactic, and the risks of transmission are reduced if the donor has taken quinine or other antimalarials regularly. Dried plasma and serum prepared from malarial blood are safe.

Hutton and Shute demonstrated that malaria parasites may survive for days, or even weeks, in blood stored at low temperatures—about 4° C.

In Cairo, severe, and even fatal, subtertian malaria was recorded by Biggam in heroin drug addicts from indiscriminate use of unsterilized syringes containing congealed blood. Similar instances have been recorded in New York by Appelbaum, Gelfand, Helpern and Most, and especially on the Pacific Coast, as well as in Peking by Chung and colleagues, and in Lisbon (Oliveira and Freire). Boyd and Slackman stated that the mortality rate amongst drug addicts may be very high. Helpern recorded 49 cases, of which 27 died.

Similarly, virulent subtertian malaria may be transmitted by unsterilized needles in intravenous injections of salvarsan, as recorded by Wenyon (1918) and Black (1939). An accidental infection from autopsy with subtertian is recorded by Holm (1946).

Transmission of malaria to the fœtus.—Congenital malaria is rare. Possibly the infection takes place by a mechanical tear, or placental hæmorrhage, by which the parasites gain entrance to the fœtal blood. Lopatin suggested intra-uterine emigration of infected maternal erythrocytes into the fœtus as a result of damage to the maternal blood vessels. Congenital malaria has long been known in Turkey as "gigli sitma"—hidden or secret malaria.

Congenital malaria, though many authentic instances have been reported, is on the whole a rare event. There is general agreement that this is not normal, but that it is due to some breakdown in the protective barrier of the placenta which, through the intimacy of the maternal and feetal bloodstream, permits the parasites to pass. This may be due to small infarcts or capillary lesions. It may, however, be due to pathological changes in the placenta as a whole as the result of overwhelming malaria infection. Thus Blacklock and Gordon in Sierra Leone found malaria parasites (P. falciparum) in the maternal blood spaces in 38 per cent. of parturient women, yet in not a single instance could they be

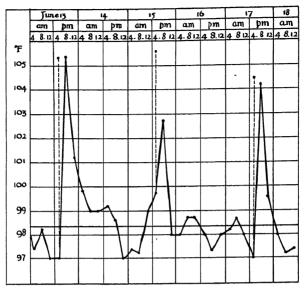
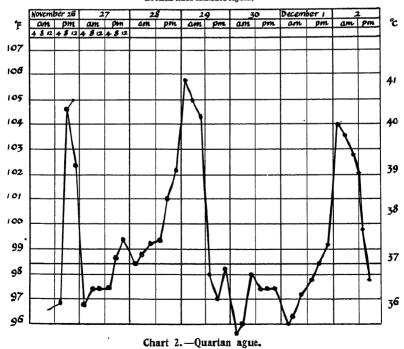


Chart 1.—Benign tertian ague.
Broken lines indicate rigors.



demonstrated in the feetal blood; though of children born of mothers with infected placentæ one quarter died within one week after birth.

Premature placental separation is suggested by the case of Tanner and Hewlett (1935) as occurring in the second of binovular twins. The commonest form is benign tertian (*P. rivax*) ranging from 16 days to 2 months after birth (Brown, 1924, Gammie, 1944). Subtertian parasites have been found in the blood of a premature child by Buckingham and crescents of *P. falciparum* in the blood of an infant of seven days (Heiser). Others have been reported from Paris (Bindeau) and Italy (Pozzioli). In Ceylon transplacental infection of the fœtus appears to be comparatively frequent (Wickramasuriya).

The four forms of parasite and associated fevers.—There are four clinical types of malarial disease which are associated respectively with four distinct species of malaria parasite. These species have been classified according to: (a) the duration of their respective life-cycles inside the human body; (b) their morphological characters; (c) the clinical phenomena to which they give rise; and (d) the results of inoculation experiments.

Benign parasites are of three kinds: the quartan, which has a cycle of seventy-two hours and causes a fever that recurs every fourth day, counting from the first day of fever—quartan fever; the benign tertian parasite, with a cycle of 48 hours, causing a fever which recurs every third day, counting in a similar way—tertian fever; and the ovale tertian which in many respects resembles benign tertian. The malignant or subtertian is also known as the astivo-autumnal, and has a life-cycle of approximately 48 hours (see Table I).

Morbid anatomy and pathology of malaria.—The pathology of malaria is based upon subtertian infections (P. falciparum). Lesions in the internal organs are due to the invasion and distribution of the infected red blood corpuscles with consequent loss of oxygen carried to the tissues. The changes in the vascular flow within the organs result from systemic disturbances, such as vascular collapse, obstruction of small vessels by auto-agglutination, thrombosis, infarction and similar effects due to clumping together of parasitized red cells. All these factors tend to slow down the circulation and cause "sludging" (Knisely). This is thought to be due mainly to the production of a fibrin-like substance. Cardiac and vascular failure (medical shock) result from these changes. There are, moreover, explosive discharges of protein from liberated merozoites and disintegrated products of red cells, destroyed parasites and extrusion of pigment.

Spleen.—The spleen, when grossly enlarged, is popularly known as the "ague cake." Although it fluctuates in size it is most certainly always swollen during an acute attack. The surface is dark, sometimes almost black and, on section, dark-red, purple or chocolate-black from congestion and pigmentation. In subtertian infections the parenchyma is so softened as to be almost diffluent, the capsule being tightly stretched. The pulp is so tarry that it can be washed away by a gentle stream of water; it is diffluent and the Malpighian bodies appear pale grey. In chronic cases perisplenitis may develop from stretching or tearing of the

capsule which may then easily rupture spontaneously or from violence. Its weight varies enormously according to the duration and intensity of infection. Clark estimated the normal spleen in negroes at 140–160 grm. (5–6 oz.) and decided that it must exceed 300 grm. (11 oz.) before it can be reasonably detected by palpation during life. In the chronic stage there is fibrous replacement. The Malpighian bodies diminish in size, standing out as pale spots against the dark background, and the pigment becomes scattered throughout the organ.

Microscopic appearances.—All stages of the parasites can be found in the red cells (in subtertian as well as in benign) and merozoites free in the pulp, but there are more parasites in the spleen than in any other organ. Malaria pigment is free in the tissue spaces and within the reticuloendothelium, and especially in the mononuclear cells. Other blood pigments are present, but there is none in the Malpighian bodies. In acute cases the reticuloendothelial system is blocked with pigment and in the later stages this is replaced by fibrosis which may obstruct the flow of blood, whilst areas of thrombosis and hæmorrhagic necrosis occur. The venous sinuses are dilated and parasitized cells in the capillaries tend to adhere to the endothelial cells and thus increase the blockage of the lumen.

Liver.—The liver is usually congested, enlarged, pigmented and olivebrown, especially in the left lobe which receives the splenic blood. Glisson's capsule, surrounding the portal system, is stretched. In chronic malaria there is some fibrosis and round-cell infiltration originating, it is thought, from the cryptozoic stages of the parasites (see p. 897). Later the congestion is accompanied by involvement of the central portion of the lobule, so that it may resemble the nutmeg liver of heart failure. The slaty-grey colour is due to pigment deposits. The organ is more solid due to the increase of endothelial cells, whilst pigment is still located mainly in the outer zone of the lobules, but also in the histiocytes and connective tissue of Glisson's capsule.

Microscopic appearances.—Parasites in all stages are found in the sinusoids and in the invaded red cells. The parenchyma cells do not usually take up malaria pigment, but the products of the destruction—hæmosiderin and bilirubin. Overactivity, following lysis of red cells leads to obstruction and over-distension of the bile canaliculi which are frequently found stuffed with bile pigment. The Kupffer cells of the reticulo-endothelium contain hæmozoin and become hypertrophied, obstructing the blood flow. The parenchyma cells show all stages of degeneration and in severe cases widespread areas of focal necrosis around the central vein. Usually the cells show cloudy swelling with granular contents and diffusely-staining nuclei. Small hæmorrhagic areas may also be present. Sometimes also congestion results from right heart failure.

Malaria pigments.—Hæmosiderin contains ionizable iron, "hæmozoin". Malaria pigment (a compound of hæmatin) contains non-ionizable iron, so that the former does not give the Prussian blue reaction with potassium ferrocyanide, unless first acted upon by nitric acid and hydrogen peroxide.

Kidneys.—Albuminuria is common in malaria, may indicate more than a simple "febrile albuminuria," and may presage serious kidney damage. This is specially the case in subtertian and quartan infections.

Sometimes there is actual azotæmia with rise of blood pressure and

cardiac hypertrophy.

In more severe cases the lumen of the tubules is filled with granular casts and fatty changes which resemble parenchymatous degeneration. Signs of glomerulonephritis are sometimes present which accounts for the rarity of azotæmic symptoms. Surbek (1981) in "quartan nephrosis" found occasionally enlarged pale white kidneys of degenerative parenchymatous nephrosis.

Heart.—The changes found in subtertian malaria are ædema due to cardio-vascular failure, "phanerosis"—increase of visible fat in the form of droplets—without increase of the total fat. Sometimes there is also necrosis.

Bone marrow.—The yellow and adipose tissue are very vascular; the red marrow is chocolate brown, especially at the periphery, due to deposits of pigment. Phagocytosis occurs with pigment containing macrophages and parasitized cells are present in large numbers, especially immature crescents. In chronic cases the reticuloendothelium is hypertrophied.

In the bone marrow there is normoblastic response; occasionally megaloblasts may be seen and reticulocytes are increased in the peripheral blood.

Pancreas.—Often there is focal necrosis, affecting especially the nutrient vessels of the Islets of Langerhans. Rarely the picture of acute homorrhagic pancreatitis may be produced.

Suprarenals.—Are specially attacked in subtertian infections. This results in partial or complete loss of the yellow colour (lipoids) of the cortex, congestion and blockage of vessels with parasites, which is held responsible for algid symptoms.

Placenta.—The maternal sinuses are packed with parasites, so that nutrition of the fœtus is interfered with. Inoculation with malaria may occur at birth (possibly through the umbilical cord or placental tear).

Stomach and gastro-intestinal tract.—The mucosa is coated with mucus and there is gastro-intestinal catarrh. Therefore, achlorhydria is common in the acute stage of malaria, and this may account for the dyspepsia and gastro-intestinal irritation. The blood capillaries are loaded with parasites, and degenerated areas of mucous membrane are encountered which may give rise to dysenteric symptoms.

Central nervous system.—The brain has a leaden hue due to deposition of malaria pigment and parasitized cells in the capillaries. Often there are punctiform hæmorrhages in the subcortical zones, especially in the corpus callosum. On the whole, the grey matter is smoky grey while the white matter is speckled with punctiform hæmorrhages. The smaller capillaries become completely blocked with parasitized cells adhering to the endothelium. In areas where there are actual hæmorrhages, macrophage cells abound, but the extravasated cells do not contain parasites. "Malarial granulomata" are focal degenerations in the brain substance, the result of hæmorrhages. Granuloma is really an incorrect term, for these lesions somewhat resemble tubercles and are formed by an agglomeration of glial cells around a central focus of degeneration (Fig. 5).

Three types of cerebral malaria can be distinguished on pathological grounds.

- (1) Massive infection.—The capillaries are blocked and thrombosed. As Maegraith has pointed out, thrombosis takes place only in fatal cases. In the clinical state the vascular condition in the brain is explained by "sludging." There are numerous small hæmorrhages with "granulomata" in the subcortical zones. Clinically there is a gradual onset of mental disturbance ending in coma.
- (2) Generalized toxamia.—This is characterized by fits and convulsions. There are scattered small hæmorrhages. Quinine has no effect and may actually increase toxicity by massive destruction of the parasites.
- (3) Embolism.—Emboli produce punctiform hæmorrhages, especially in the corpus callosum.

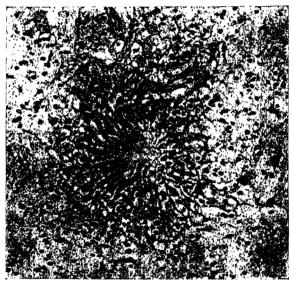


Fig. 5.—Malarial granuloma. Brain section showing plugging of capillaries of cortex and proliferation of glial cells. (Dürck-Archiv für Schiffs- und Tropenhygiene.)

Clinical pathology.—The loss of parasitized cells resulting from sporulation is governed by the degree of infection of the red cells, being most severe in subtertian and least in quartan.

There is also lysis of non-parasitized cells, but this does not appear to be due to any known circulating hæmolysin or to fragility in saline, but the cells in malaria and blackwater are sensitive to lysolecithin systems, suggesting some alteration in their surface properties.

Autoagglutination—an increase in α and $\hat{\beta}$ agglutinins—may play a part in hæmolysis. At the time of sporulation oxyhæmoglobin and methæmoglobin are thrown into the circulation as a result of red-cell destruction. Under ordinary circumstances such pigments are absorbed by the reticulo-

endothelial system, but when lysis is extreme these pigments may be thrown into the urine. In severe cases a combination of albumin and hæmatin may be formed which does not pass through the kidneys and is known as methæmalbumin. In established anæmia the blood cells show polychromasia, basophilia, poikilocytosis, and anisocytosis. In severe cases normoblasts and sometimes megaloblasts are seen. Basophilic stippling persists after disappearance of malaria parasites and may be regarded as evidence of persisting malaria infection. Megaloblastic changes have been reported in the bone marrow. Reticulocytosis occurs in the bone marrow and less so in the peripheral blood, especially after institution of specific therapy. Autoagglutination in subtertian malaria may be related to the "stickiness" of the parasitized red cells. Complement fixation bodies exist and can be shown by using antigens prepared from the spleen or from suspensions of malaria parasites.

Leucocytes.—There is frequently a leucopenia associated with increase of the large mononuclear cells, but this leucopenia is not characteristic of malaria. Some may show a leucocytosis, especially when there is some secondary infection, such as pneumonia and this possibility must be borne in mind. The white cells frequently contain malarial pigment which is usually found in the monocytes, but sometimes in the polymorphs. Such pigment-containing leucocytes are indicative of a very recent infection.

CHEMICAL CHANGES IN THE BLOOD

Blood proteins.—The reduction in total plasma protein is mainly due to reduction in albumin and there is usually an increase in globulin. The albumin-globulin ratio is therefore altered. Therapeutic malaria is followed by a return of protein to normal in a process which takes three weeks. These changes are not due to the fever alone, but are associated with upset of liver function which occurs in malaria.

Cholesterol and lecithin.—There is hypo-cholesterolæmia during malaria, but it may rise during the rigor and fall to subnormal in the apyrexial periods, so that further investigation of lecithin-changes may shed light

on the mechanism of hæmolysis.

Blood sugar.—As glucose is essential for the respiration of plasmodia changes in the blood sugar are to be expected. Sinton reports a rise in blood sugar during pyrexia in both P. vivax and P. falciparum. It is suggested that this rise may be associated with change in liver or adrenal function.

Inorganic elements.—Plasma potassium is raised in febrile persons and is at its height during segmentation, but in low grade or chronic malaria there may be no change. The rise of potassium in acute malaria is probably due to destruction of red cells.

Physical changes.—The E.S.R. is increased in malaria and is restored to normal after treatment. The degree is dependent upon the protein content of the plasma and the activity of the surface of the cells. The fall of protein in the blood may be such that the permeability of the vessels is affected and the osmotic pressure of the plasma reduced.

pH and alkali reserve.—As parasites use glucose for respiration it is possible that pyruvate and lactate may accumulate under conditions of

anoxia, such accumulation would result in a fall of pH and loss of alkali reserve. Acidosis is exceptional.

Polycholia.—Up to a certain point in pathological hæmoglobinæmia the liver is capable of dealing with liberated hæmoglobin, so that, when this pigment is set free in the blood, serum secretion and flow of bile (bilirubin) are correspondingly increased.

Liver function in malaria.—Clinical signs of liver dysfunction have been recorded in all forms of naturally-acquired malaria as well as in the therapeutic induced disease, but they are most pronounced in certain forms of *P. falciparum*. Enlargement of the liver following the paroxysm

is comparatively common.

Lichtman (1942) has described six cases of extensive hepatic necrosis. In course of review of 1,158 cases Kern and Norris (1944) reported 59 had enlarged livers, abnormal Van den Bergh reactions and raised serum bilirubin. The results of bromsulphthalein retention tests were in accordance with other abnormal findings. Kleeberg and Birnbaum (1947) have investigated the Weltman reaction in *P. vivax* and *P. falciparum* malaria. This reaction measures the coagulability of the patient's serum in solutions of calcium chloride which is governed by the globulin content. There is a close relation between the changes in the coagulation of the serum in lower calcium concentrations and the sensitivity of the erythrocytes to lysis in bile solution indicating hepatic damage.

Dole and Emerson (1945) find that during the malarial attack the total proteins of the serum remain within normal limits, but the albumin/

globulin ratio is depressed.

Bile is not found in the urine unless there is frank clinical jaundice. Urobilin and urobilinogen excretion has been fully investigated by Kingsbury (1925). He found that it did increase in malaria, especially in subtertian, but it is not of absolute diagnostic value.

The prothrombin content of the blood is not changed in the febrile period because there is thrombocytopenia, as reported by Maslova (1942) who found decrease in blood platelets and lessening of coagulation time during a malarial rigor. It is therefore clear that deviations in the so-called hepatic function tests occur in both naturally-acquired and therapeutic malaria.

THE CLINICAL PICTURE

Symptoms of malaria.—An attack of malaria may either be a primary attack or a relapse. Conjunctival ecchymoses have been described as an early complication of benign tertian malaria in British troops, usually between the 3rd and 7th days. These ecchymoses rapidly spread to cover the lower half of the sclera. A primary attack normally develops after an incubation period of 10–14 days, but when blood is used for inoculation, the incubation period varies from 48 hours to one month, depending upon the numbers of living parasites injected. By direct blood inoculation it is about 11 days. In insect-transmitted subtertian malaria, where the number of infecting bites is increased, the incubation period tends to be shorter and may only be five days. Sometimes the incubation period may be prolonged; thus some artificially infected with benign tertian may

show no clinical signs or exhibit parasites in the blood for as long as nine months and similar long periods are often seen in patients leaving the endemic area. This is known as latent malaria. In subtertian malaria it is possible to have a primary attack in the absence of any noticeable symptoms, but there is no latency in the same sense as in benign tertian. The type of temperature curve, whether intermittent or remittent, is less significant than formerly considered to be the case. Thus primary benign tertian infections may produce a remittent temperature curve before assuming the classical intermittent character. Two or more generations of tertian parasites, maturing in the blood at different times, will produce quotidian fever and two generations of quartan will give a fever on two successive days—quartona duplex—or conversely on three successive days, a quotidian fever—quartana triplex.

Relapses are defined as recurrences of malarious symptoms and the reappearance of malaria parasites in the peripheral blood, following recovery from the initial attack. Therefore relapses must be distinguished

from reinfections.

Recrudescences of malaria are defined as relapses of the patient at the time he is removed from the endemic area. Relapses often follow the cessation of suppressive treatment, exposure to cold, exertion, parturition, or surgical operations. Benign tertian and quartan relapse most frequently. Reinfections do not show the remittent character of the primary attack, but assume tertian or quartan classical forms.

The characteristic ague is divided into three stages: (1) cold stage, (2) hot stage and (3) sweating stage. One or even all these stages may be absent on occasions, especially when the infection is of long standing, whilst in subtertian fever many symptoms are so bizarre that they may be most misleading, so as to enforce the conviction that in many respects it is quite a different disease.

Herpes on lips and nose (fever sores) often extensive, frequently follow the rigors and is an accompaniment of all forms of malaria. Similar eruptions have been noted on the ears.

Premonitory stage.—For several days before the actual attack the patient may be conscious of headache, lassitude, a desire to stretch or yawn, aching in the bones, anorexia, sometimes vomiting.

Cold stage.—This usually lasts one to two hours, and is the rigor, or "ague." The feeling of cold is intense and universal. The teeth chatter; the patient shivers from head to foot and wraps himself up in any garment he can lay his hands upon. Vomiting may be most distressing. The features are pinched, the fingers shrivelled and the skin blue like "gooseskin" (cutis anserina). The feeling of cold is purely subjective, because the temperature is rapidly rising. Children usually have convulsive fits.

Hot stage.—The hot stage may last from three to four hours. The shivering abates and gives place to, or alternates with, sensations of great heat. The clothes are thrown off. The face is flushed; pulse full, bounding and usually dicrotic; headache intense; vomiting usual; respiration hurried; skin dry and burning; the temperature rising to 104°, sometimes 106° F., rarely higher.

Sweating stage.—This usually lasts from two to four hours. The patient breaks out into profuse perspiration with sweat literally running off him in streams, saturating clothes and bedding. With sweating the fever rapidly declines. Headache, thirst and distress give place to a feeling of relief and tranquillity. When it has ceased the patient may feel exhausted, but quite well and able to go about. The body temperature is now subnormal and remains so until the approach of the next paroxysm, one or two days later.

Duration of fever fit.—The total duration of the fever cycle may be from six to ten hours.

Urine and fæces in ague.—During the cold stage the urine is abundant, limpid and micturition frequent; during the hot sweating stages it is scant, cloudy, sometimes albuminous. Urea excretion is increased during the rigor and hot stages, and so is that of the chlorides and sulphates. Phosphates, on the contrary, diminished during the rigor and hot stages, are increased during defervescence. Augmentation in urea excretion commences several hours before the attack, attains its maximum towards the end of the rigor, and decreases during the terminal stages, though still above the normal figure.

A fleeting glycosuria has also been observed from time to time. Rarely a picture of true diabetes with increased blood sugar may be produced as in a case reported by Rau (1948). This is due to infection of the blood capillaries of the islets of Langerhans by P. falciparum. The urine usually contains urobilinogen and urobilin in excess during the attack, but they decline with the temperature. This is a valuable diagnostic sign, especially in subtertian malaria. The corresponding pigment in the fæces (hydrobilirubin) is increased twenty times the normal

amount whilst parasites persist in the blood.

The spleen during ague.—The spleen is enlarged and painful during the rigor, but in early infections not always palpable. This has been specially noticeable in the recent war in India and Burma and the statement applies to benign as well as subtertian infections. At first the enlargement recedes during the interval, but it tends to become chronic if relapses or re-infections are numerous, especially when associated with pronounced cachexia. This does not constitute the whole explanation; in primary cases the spleen is very soft and spongy, therefore difficult to palpate. In relapses it becomes harder and more fibrous. Sometimes when a patient is in bed the spleen remains soft, but becomes harder when he gets up. Spontaneous and fatal rupture may occur in benign tertian as well as in subtertian infections, more usually as a result of direct violence (de Saram and Townsend, 1943). A successful splenectomy does not, as has often been stated, extirpate the malarial infection. procedure is to be deprecated as it has been demonstrated in P. knowlesi in monkeys that immunity is thereby destroyed and some think that after splenectomy malaria acquires increased virulence.

Hennessy and others have recorded that splenic rupture, through causing severe internal hæmorrhage, may produce misleading symptoms which may

mimic those of rupture of the bladder by causing urinary irritability and hypogastric pain. There is often a latent period with absence of symptoms (Fry). Referred pain to the tip of the left shoulder is known as Kehr's sign. In the early stages it is present in a small proportion of cases. Galloway noted that a pain moving from the uppermost shoulder to the one on which the patient is recumbent is a marked feature. Changes in the left lung base may serve as an aid to diagnosis. The histopathology of these friable spleens (Lubitz) shows that a subcapsular hæmatoma precedes rupture and leads to capsular tear. In acute malaria small hæmorrhages occur in the vicinity of the capsule or deep in the tissues. There is diffuse cellular hyperplasia, with dilated sinuses, and occasional thrombosis and infarction.

Johnston Abraham has described a secret murder weapon employed by Dyaks in Celebes. The weapon resembles a child's wooden dagger 8 in. in length. The cross-bar is concealed in the clenched palm of the hand, a portion is strapped round the wrist and the weapon can be concealed in the sleeve of the jacket. This weapon is used to strike a heavy concentrated blow over the enlarged spleen so as to show no external sign of violence.

An important lesson for clinicians is that failure to palpate the spleen should not justify omission of microscopic blood examination for malaria parasites.

Shepherd (1946) describes a radiographic technique for demonstration of the spleen without use of a contrast medium. The product of the length and breadth of the shadow of the spleen (measured in inches) is called the *radiographic splenic index*. The upper limit for the normal radiographic spleen is an index of 8. That for the earliest degree of enlargement which could be detected clinically was $9\frac{1}{2}-10\frac{1}{2}$. It is concluded that, in cases in which the clinical diagnosis remains doubtful and blood films negative, this radiographic splenic index may be of diagnostic value.

Period of the day at which ague commences.—Quite a large proportion of agues "come off" between midnight and noon or in the early afternoon. This time factor may constitute an important point in diagnosis, especially as pyrexial attacks somewhat simulating malarial agues may be caused by liver abscess, tuberculosis, Bact. coli infections of the urinary tract and septic conditions, in all of which febrile recurrences are apt to take place during the afternoons or evenings. (This rule does not obtain in therapeutic malaria where Kitchen has found two-thirds of the paroxysms occur from 3 p.m.—8 p.m. and only 8.7 per cent. from 1 a.m. to midday.) The fever in meningococcal septicæmia may show a tertian or quartan periodicity difficult to distinguish from malaria.

Atypical agues.—There is an infinite variety of what may be termed "masked malaria," that is to say, malaria without the more easily observable manifestations, especially in subtertian infections, which are apt to become pernicious. There may be a comparatively slight rise of temperature with supra-orbital neuralgia, headache, prostration, vomiting, or gastric oppression and dyspeptic symptoms.

In benign tertian in the initial stage of a primary attack, the fever is quotidian and remittent in type, rarely exceeding 103° F. (39.4° C.), and is unaccompanied by rigors. At this stage it should be noted that parasites are extremely scanty in the circulation. In the fully developed stage the fever becomes intermittent and the peaks of temperature become higher

whilst each paroxysm is accompanied by a rigor. On blood examination numerous asexual parasites in all stages of development from young rings to mature schizonts are present in the peripheral blood. In *relapse* the fever is definitely tertian periodic. Asexual parasites in same stage of development are present in the peripheral blood.

Course of benign tertian and quartan fevers.—Benign tertian ague usually lasts ten hours or less and may be taken as the type of a malarial attack. In some cases the rise of fever is rapid and high, and the temperature may reach 105° to 106° F. within an hour or so; on the other hand, in some cases none of the clinical phenomena are present and the temperature does not rise above 99–100° F. Benign tertian, unless complicated, is not usually fatal; but the persistent and relapsing character makes it a tiresome disease and, if prolonged, may produce severe anæmia and debility.

Certainly many strains of P. vivax seem to exist which differ in their virulence: some are mild, as in Holland; sometimes the fever is trivial and isolated attacks, without recurrence, are common enough. strains of P. vivax have been found to possess distinctive characters and vary in the number and frequency of the relapses they produce; for instance the virulent New Guinea strains of Fairley and the "Chesson" strain of American workers which tends to relapse every six weeks which may be compared to the "benign" St. Elizabeth strain from America and the Madagascar Horton strain which may not relapse for several months. This is the typical relapsing malaria and it is probable that the tendency to relapse depends upon the strain of the parasite and rapidity with which tolerance is acquired. James (1930) has defined in this fever a recrudescence as the return of fever and parasites within eight weeks of recovery from the primary attack: relapse as a return of fever and symptoms between the eighth and twenty-fourth weeks and recurrence as a return later than this This classification has been generally accepted.

The presence of a rigor appears to be an index of severity, and the mean parasite density has been stated by Kitchen, on the first day of rigor, to be 4,012 per c.mm. The mean maximum temperature for the paroxysms is 104.2° F. As a general rule, the duration of a simple benign tertian infection before the parasites die out from the peripheral blood is nine months to one year after leaving the endemic area, but exceptions to this rule occur, as clinical relapses, with parasites in the blood, have been recorded as long as three years after the original infection. As it is seldom fatal the pathology is not so well-known as that of subtertian malaria, but it resembles it in a minor degree. This form of malaria reacts readily to quinine, atebrin, paludrine, plasmoquine, chloroquine and daraprim, but the parasites are difficult to extirpate. Initial remittent stage less frequent.

In the endemic areas the quartan parasite is most frequently found in children. The reason for this has not been definitely ascertained.

The fever in quartan malaria is generally smart while it lasts, and is well-defined in its various stages, but it does not produce much systemic disturbance or cachexia or rigors. It has often been remarked that,

whilst individual attacks of this infection are amenable to quinine and atebrin, the disease is more persistent than tertian or subtertian, so that attacks are apt to occur from time to time over a period of many years and may persist as long as 12 or even 21 years (Shute). It is becoming increasingly realized that sometimes quartan parasites may be present in the blood without evoking any special symptoms. Parasites are usually scarce in the peripheral blood. They are more resistant to anti-malarial drugs in the sense that they persist in the bloodstream for a week or more while the patient is taking the drug.

Quartan periodicity is the hall-mark of quartan malaria and is hardly ever found in any other disease. Double quartan and triple quartan fevers may be observed. In the latter the temperature course becomes quotidian. Occasionally, quartan fevers are encountered without splenomegaly and apparently when parasites cannot be found in the blood; their true nature can be ascertained solely by the action of quinine by injection.

Quartan malaria nephrosis.—Although kidney changes are associated with subtertian malaria, nephrosis is commonest in countries

where the quartan parasite predominates.

According to Giglioli both sexes are susceptible, and especially children, in whom quartan malaria is most common, but in adults males predominate. He regarded albuminuria in a febrile attack as an indication of parenchymatous nephritis; Goldie, on the other hand, took a less serious view and considered the pathological picture as one of nephrosis and due to the production of malarial toxins over a long period. The special liability in quartan is to be ascribed to insufficient initial treatment on account of the all too frequent non-recognition of this infection due to its mild character. It is thus much more liable to relapse into the chronic stage. The nephrosis declares itself by generalized cedema and the passage of decreased urine containing albumin and casts. The blood urea is not necessarily raised.

Course of ovale tertian malaria.—This type closely resembles the benign tertian in its periodicity; but, generally speaking, the attacks are sudden, short and mild, and not accompanied by any grave degree of anæmia, whilst the rigors are more apt to take place during the evenings. Rheumatic-like pains in various parts of the body, especially the lumbar region, are characteristic, and sometimes pain referred to the appendix may suggest appendicitis. There is usually no excess of urobilinogen in the urine. Occasionally severe infections are encountered, but when the patient is really ill it is often superimposed on other infections, such as the subtertian. It may evince considerable latency. There is an initial remittent stage in less than 50 per cent. Rigors are less frequent than in *P. vivax* and spontaneous recurrence is uncommon.

Course of subtertian or malignant malaria.—From the clinicians' viewpoint this is the most important form of malaria. It differs from the others primarily in the greater toxicity and greater variety of symptoms which it may evoke. It may appear in trivial form or rapidly develop into a dramatic and rapidly fatal disease.

There are probably many strains of *P. falciparum* differing from one another in virulence as James has shown with his Sardinian strain. Herpes labialis is commoner with this form.

In distinguishing subtertian malaria the rigor stage is relatively less marked, or may be absent entirely. The primary attack begins with a sense of chilliness. The hot and sweating stages are more prolonged and liable to be followed by an adynamic condition (see p. 56), together with

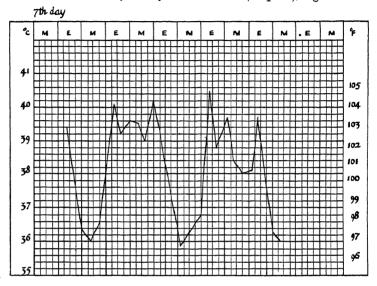


Chart 3.—Subtertian fever (P. falciparum).

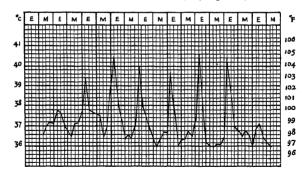


Chart 4.—Quotidian fever (two generations of P. falciparum).

vomiting, intestinal irritation, bone pains, anorexia, headache and supraorbital neuralgia and a degree of moderate sweating. After apparent recovery from fever there is a tendency to recrudescence at shorter intervals than in benign tertian. Subtertian fevers are accompanied by rapid hæmolysis, toxæmia and succeeded by marked cachexia. The underlying pathology is due to the sporulation of parasites in the internal capillaries and relative blood-stasis owing to the stickiness of the infected red cells which tend to agglomerate and also to iso-agglutinins in the serum, so that at any time during the course, and especially in primary infections, symptoms of the gravest character may appear. The tendency for successive paroxysms to overlap, or to become subintrant, is marked. When intermissions are distinct the crisis is what is called "a double crisis." Thus, when the fever has attained its apparent fastigium, there is a drop of one or more degrees of temperature—a false crisis—followed by a fresh rise which is then succeeded by a true crisis. This peculiar phenomenon has been attributed to the presence of two generations of parasites in the blood, one of which matures somewhat later than the other; it occurs ordinarily in one other tropical fever: kala-azar (Chart 3). Such an infection may therefore produce a quotidian typhoid-like temperature chart Chart 4). Even at this stage the temperature may not exceed 103° F. or 104° F. (39.4°-40° C.). Hughes and Bomford (1944) pointed out that in milder clinical forms there is usually a relative bradycardia.

Though this fever may be justly regarded as dangerous to life, yet it is singular that subtertian parasites may exist in the blood for months without seriously interfering with health. Then an explosion may occur, brought about by exposure or fatigue, with dire results, or, it may be, with blackwater fever. Sometimes attention is drawn in other directions—to edema of legs, diarrheea, dyspepsia or some other apparently small complaint, quite unconnected with malaria, and these may appear in men returning from West Africa in whom the first symptoms of ill-health may be noted after several weeks' residence in a temperate climate.

On the whole, though dangerous to life, the subtertian parasites (in the trophozoite or ring form) are more amenable to anti-malarial drugs than are the benign tertian, though larger doses are required to cut short the initial attack. Moreover, the lifespan of this species in the human body is much shorter, lasting nine months to one year after leaving the endemic area of this disease. The clinical forms which subtertian malaria may assume are so many that it may simulate many other tropical fevers, even mimicking surgical emergencies. Myalgic types, with muscular pains and stiffness, and gastric types, with vomiting and gastro-intestinal symptoms, are frequent in the milder forms. In the acute, as well as in the chronic stage, spontaneous and fatal rupture of the spleen may take place.

Manson said, and it is particularly apt, "What one sees in the peripheral circulation is only a reflection of the drama which is occurring in the internal circulation."

Bilious remittent.—One type of subtertian fever—bilious remittent—has long been recognized on account of the bilious vomiting, gastric distress, sometimes bilious diarrhea, sometimes constipation, which accompany the recurring exacerbations. It is further distinguished by the pronounced icteric or, rather, reddish yellow or saffron tint of skin and scleræ—a tint derived, probably, not from absorption of bile as in obstructive jaundice, but from modified hæmoglobin (serum bilirubin) free in the blood or deposited in the skin and sclerotics. Sometimes cases are seen with intense icterus, high serum bilirubin and jaundiced scleræ.

¹ Similar clumps of erythrocytes have been observed in monkeys infected with *P. knowlesi* and their dispersal with atebrin therapy (Knisely).

without splenomegaly, but with large numbers of parasites in the peripheral blood. This type may be readily mistaken for various forms of obstructive jaundice.

A modification of the bilious remittent—the "typhoid remittent"—is very much more grave, as affecting life, than the simple bilious remittent. In the typhoid remittent, typhoid symptoms—such as low delirium, prostration, dry tongue, swelling of spleen and liver, subsultus tendinum—are superadded to the usual symptoms. Though recovery is the rule, a considerable proportion of such attacks prove fatal.

Pernicious attacks.—The French neatly designate these accès pernicioux. They characterize subtertian infections, and may supervene in apparently mild cases and carry off the patient with horrifying suddenness—as suddenly as an attack of malignant cholera. Pernicious attacks are apt to develop in drug addicts (see p. 40). They are classifiable into: (1) septicænic (or toxæmic) type, accounting for about 30 per cent., with numerous parasites in the blood, death taking place from cardiac failure; (2) cerebral, accounting for some 55 per cent., ending usually in coma, in which, compared with other forms, parasites are usually very scanty in the peripheral blood; (3) algid, with subnormal temperatures and a clinical syndrome resembling that of shock, accounting for some 14 per cent., and finally (4) renal, with cedema and nephritic signs which, though rare, amount to about 1 per cent. of the total.

Cerebral forms.—In the course of what seemed to be an ordinary malarial attack the body-temperature, instead of stopping at 104° or 105° F., may continue to rise and, passing 107°, rapidly mount to 110° (or even, rarely, to 112°). The blood shows hyperinfection with P. falciparum and more than 5 per cent. of erythrocytes are infected and most contain about two parasites in each corpuscle. The patient, after a brief state of maniacal or, perhaps, muttering delirium, becomes rapidly unconscious, then comatose, and dies within a few hours, or perhaps within an hour, of the onset of the pernicious symptoms. The skin is hot and burning. Fever sores (herpes labialis) are often observed around the lips and mouth. There is an almost distinctive facies. The pulse is rapid and dicrotic, and there may be generalized muscular twitchings. Splenic pain may be prominent. At first there is disorientation with motor aphasia. Incontinence is usually a dangerous sign.

Coma.—Sometimes the patient, without hyperpyrexia (the temperature perhaps not rising above, or even up to, 104°), may lapse into coma. The coma may pass away with a crisis of sweating; on the other hand, an asthenic condition may set in and death supervene. There is often a paralytic squint, extensor plantar response and Cheyne-Stokes respiration. When subcortical hæmorrhages are present, death usually ensues. There is a marked increase of pressure in the cerebro-spinal fluid, with increase of lymphocytes up to 400 per c.mm., as well as of albumin and globulin. Occasionally, granules of malarial pigment may be found. It is important to note that parasites may be very scanty in the peripheral blood and not infrequently they appear to be absent altogether.

Marriott (1945) has classified the symptoms as follows:— Cerebral depression.—All stages from drowsiness to deep coma. Cerebral excitation.—All stages from mild excitement and talkativeness to extreme restlessness and mania.

Behaviour changes—character alterations.—Irritability, and depression developing in a previously well-balanced personality. Psychotic symptoms are not uncommon.

Meningismus closely simulating meningitis and focal nervous lesions resulting in dysphagia, diplopia, etc. Sometimes a focal spine lesion may

cause paraplegia.

Epileptiform attacks.—There has been some divergence of opinion about the origin of epilepsy following malaria. Mohr thinks that symptoms of meningitis, as the result of damage of brain substance in corobral malaria, may arise, including epileptiform attacks.

These cerebral attacks depend upon embolism by sporulating subtertian parasites in the capillaries of the various nerve centres: in hyperpyrexia, the thermic centres are involved; in aphasia, Broca's convolution. Monoplegia or hemiplegia may result from implication of various brain areas. Viswanathan has demonstrated thrombi in the sagittal sinus and considers that this is a factor of considerable importance.

Malarial amblyopia.—In rare instances a comatose pernicious attack ends in blindness. The amblyopia is usually transient, lasting for an hour or two only. On the other hand, it may be persistent; in which case optic neuritis, peripapillary edema, extravasation of leucocytes, plugging of retinal and choroidal vessels by parasites or pigmented leucocytes, and consequent multiple hæmorrhages, may be found in the fundus. The disc itself is rosy or cherry-pink in colour, which is considered diagnostic. If the hæmorrhages are minute they are discoverable by the microscope only; on the other hand, large retinal hæmorrhages do occasionally occur. There may be blurring of the edges of the discs (Appelbaum and Gelfand), and partial atrophy may follow. These fundus changes differ from those of quinine amblyopia. In the latter, depending on retinal toxic damage, the amblyopia is more persistent; the discs are usually white and the vessels shrunken; central vision is the first to recover. (In the modern literature of malaria there are very scant references to the fundus changes. Raynaud in 1892, in a monograph, described them in great detail, and de Mussy in 1872 first described retinal hæmorrhages.)

The Editor has observed hemiatrophy of the optic disc with altitudinal hemianopia in an unrecognized case of subtertian malaria. Mackay-Dick (1944) has recorded a unique complication—marked diplopia with paralysis of the left external rectus muscle due to a lesion involving the sixth cranial nerve.

Other cerebral forms.—There may be sudden delirium ending in coma and, perhaps, death; conditions simulating cerebro-spinal meningitis; delusional insanity; dementia; acute alcoholism; various forms of apoplectic-like conditions and of paralysis, complicated, it may be, with aphasia. Scizures of this description, if not fatal, may end in permanent psychical disturbances, with a tendency to suicide. Temporary debility, or even complete loss of memory, may succeed severe cerebral malarial infection.

Algid forms.—The algid forms of pernicious attack, as indicated by the name, are characterized by collapse, extreme coldness of the surface of the body, and a tendency to fatal syncope. These symptoms usually co-exist with elevated axillary and rectal temperature. Flooding of the peripheral blood with vast numbers of parasites in all stages of development—gametocytes as well as schizonts—is sometimes found. The

prognosis is usually bad, but rarely this may be seen in an attack of average severity. It indicates a continuous fever of at least two weeks, or a relapse of short duration.

Gastric form.—This may be associated with, and in a measure be dependent on, acute catarrhal dyspeptic trouble. It is accompanied by severe epigastric distress, tender retracted abdomen, and incessant vomiting. The vomited matter may contain blood.

Choleraic form.—Malarial attacks are sometimes accompanied by choleraic symptoms. The stools suddenly become loose, profuse, and numerous, but generally not so profuse or colourless as the rice-water discharge which pours from the patient in true cholera; they retain a certain amount of biliary colouring, and may be mucoid, or even bloody. As in cholera, the serous drain may lead to cramps in the limbs, loss of voice, pinched features, "washerwoman's fingers," almost entire suppression of urine, and perhaps to fatal collapse. The high axillary temperature, if present; a history, maybe, of recent ague fits; the subsequent rapid cessation of choleraic symptoms on the appearance of the hot and sweating stages; the colour of the stools, and other collateral circumstances, usually suffice for diagnosis, particularly if they are supplemented by microscopical examination of the blood. Although not usual, recurrence of the choleraic symptoms may take place at the next fever period.

Dysenteric forms.—Another form of pernicious attack is characterized by the sudden appearance of dysenteric symptoms, by severe and recurring hæmatemesis, or by hæmorrhage from the bowel or elsewhere. This possibility must therefore be kept in view; particularly if, in what at first sight appears to be ordinary dysentery, the axillary temperature is found abnormally high. Dysenteric forms are explained as due to blocking of the intestinal capillaries by masses of parasitized cells, with consequent necrosis of the mucosa.

Hæmorrhægie forms.—As in purpura, so in these pernicious attacks, hæmorrhages may occur in almost any organ. Purpuric hæmorrhages into the skin may be generally distributed over the body; they may be diagnosed by skin biopsy, and demonstration of the parasites in the capillaries. They are rare, but are commonly associated with better-known phenomena of malaria.

Œdema.—General anasarca with chronic subtertian malaria has been noted in debilitated subjects as, for instance, in war refugees in Greece and in the great Ceylon epidemic of 1934. Wickramasuriya recorded it in 40 per cent. of 357 cases specially investigated in pregnant native women. It is by no means infrequent in therapeutic malaria (Kopp) and has been regarded as due to marked reduction of the plasma proteins. This cedema sometimes disappears on treatment.

Acute hæmolytic anæmia.—There is a rapidly developing and progressive anæmia in the fourth or fifth week of a primary subtertian attack or in an untreated chronic relapse, only comparable to that seen in the most advanced stages of pernicious anæmia. These cases are characterized by great pallor of mucous membranes and conjunctive, cardiac distress, dyspnæa, hæmic murmurs, and retinal hæmorrhages; the blood-picture by a blood-count of under 1,000,000, extreme leucopenia, a reduction of

hæmoglobin to 10 per cent. or under, macrocytes and megaloblasts in the blood.

Rarer clinical forms of subtertian malaria.—Pulmonary forms have been described, with congestion of the pulmonary vessels, bronchitic symptoms or even cedema of the lungs. Rare cases with rapidly developing anasarca and ascites were observed in Macedonia and in Palestine during the 1914-18 war; and, cedematous forms with nephritic signs, such as blood-cells in the urine, have been noted. Disturbances in the vaso-motor mechanism, as in Raynaud's disease, have been recorded, and occasionally gangrene of the toes and fingers.

Orchitis in the course of a malarial attack may be due to agglomeration

of parasites in the testes (Mayer and Bastillo).

Mixed infections.—Double infections with P. vivax and P. falciparum are common and may give rise to some confusion, especially when the ring (or trophozoite) stages of both parasites are present in the blood at the same time. More usually P. vivax is superimposed upon P. falciparum, so that the patient runs through the average course of the latter, and when he has apparently recovered, relapses of P. vivax make their appearance. This late appearance, it may be after a lapse of six months or even a year, was commonly observed in soldiers infected in war zones in both 1914–1918 and in the recent war in India and Burma (1948-1945). In the endemic areas of quartan malaria—in S. Ceylon and Malaya—double infections with P. vivax and P. malarice are quite common, and in these cases the latter parasite survives longer. On one occasion the Editor found all three species in the bloodstream—P. falciparum as well as the two already mentioned at the same time, though the course of the illness was not exceptionally severe.

Malaria in indigenous inhabitants of the Tropics.—Malaria, as it occurs amongst Africans and other indigenous peoples who have been exposed to its ravages for centuries, presents a different clinical picture to that of the non-immune European. From infancy onwards he is exposed to repeated plasmodial infection and is in a state of premunition (p. 74). Acute malaria is in these people predominantly a disease of infants and young children in whom premunition has not yet been established. Pernicious complications, including cerebral malaria, account for a considerable proportion of deaths. Soon, however, in older children and adults living in the endemic area, a gradual acquisition of relative immunity becomes evident. The rise of temperature which heralds an attack is not accompanied by shivering and the whole illness is of a very mild character which hardly interferes with the day's work. Vomiting and sweating are usually absent. Verily it resembles a different disease.

In the great majority chronic malaria exists without giving rise to significant features, even though plasmodia may be present in blood smears. Thus the picture of chronic ill-health so graphically displayed by the sick European under similar circumstances is absent. Splenomegaly is almost always present and a low-grade continuous pyrexia is seldom sufficiently pronounced to interfere with the daily round, but an amemia

of a moderate hypochromic type becomes established.

Malaria in pregnancy.—Pernicious symptoms are apt to develop in pregnant women infected with *Plasmodium falciparum*. Cerebral manifestations in late pregnancy arising unexpectedly, without any previous malarial history, may cause serious diagnostic difficulties. The majority are diagnosed as eclampsia. The epileptiform attack in pregnancy is better termed "eclamptic." A lucid interval is very likely to follow intravenous quinine therapy and is apt to lead the inexperienced physician astray.

"Latent" malaria tends to persist through pregnancy, to become active during parturition or lactation. Wickramasuriya, who has adequately surveyed this subject, finds that malaria can modify the course of pregnancy by spontaneous interruption before term; indeed, malaria per se is a far more potent oxytocic than any drug, especially in the ill-nourished who are also suffering from ancylostomiasis. Intra-uterine death of the fœtus is fairly frequent, whilst clinical and pathological evidence points to malaria as a powerful predisposing factor in the toxæmias of pregnancy, such as pre-eclampsia, eclampsia, and "nephritic" toxæmia. In subtertian malaria, albuminuria and ædema of renal origin appear. Hypertension, that most important criterion of pregnancy toxæmia, is often noted. Greater dangers are to be expected when the disease occurs in the later than in the earlier months of pregnancy.

Malaria after operation.—Latent malaria is often brought out by operations and is a definite factor in retarding post-operative recovery. Parry (1946) found that wounds do not heal normally, but show a tendency to hæmorrhage. Skin grafts do not take till antimalaria treatment is instituted. Intravenous anæsthesia tends to produce cerebral malaria in infected subjects and inhalation anæsthesia broncho-pneumonia. Bodily injury, parturition or shock, may precipitate an attack of malaria in spite of regular antimalaria drug prophylaxis. The parasite concerned is usually the benign tertian.

Malaria in small children.—Malaria, especially subtertian, is a much more severe disease in children than in adults, especially in native races. Benign tertian malaria frequently produces the most alarming symptoms in babies, but it is not necessarily very severe and is easily controlled; but subtertian malaria is especially likely to assume the cerebral form and should always be regarded seriously. Amongst 138 babies examined periodically from birth onwards in Nigeria the infection rates were 3 per cent., 14 per cent. and 50 per cent. respectively and nearly 100 per cent. by the end of the first year. Malaria was responsible as the cause of death in 9 per cent. of infants dying in hospital; in 13 per cent. in early childhood; in 7.4 per cent. in the younger and 3.6 per cent. in the older age groups.

Complications.—Subtertian malaria may complicate, or be complicated by, almost any other disease; a common and very fatal terminal event is pneumonia, either lobar or broncho-pneumonic; this was noticeable in the influenza epidemic of 1918. Enteric greatly complicates the clinical picture, as do the main forms of dysentery. Pulmonary tuberculosis is very likely to supervene in cachectic cases. During recent years primary atypical pneumonia has been associated with epidemics of subtertian

malaria in the war in North Africa and Italy. The symptoms are very similar and in 30 per cent. malaria was present as well as pneumonia. Noma or cancrum oris frequently complicates severe subtertian malaria in small children in Turkey, whilst purpuric rashes and cloasma pigmenta-

tion of the face is relatively frequent.

The chief and most dramatic sequel is undoubtedly blackwater ferer. On the other hand, babies at the breast of African mothers during the first three months seldom contract subtertian malaria. This may be due to the action of the mother's milk (see p. 86). Thus Garnham in the Kavirondo district found that at the end of the third month only 10 per cent. of children were infected, thereafter the percentage affected rose rapidly so that by the end of nine months all had the disease.

BLACKWATER FEVER

Synonyms.—Malarial Hæmoglobinuria; Hæmoglobinuric Fever.

Blackwater is an exaggerated form of subtertian malaria consisting of acute hæmolysis of the red blood corpuscles which liberate hæmoglobin

into the plasma and produce hæmoglobinuria.

There are certain points of analogy between it, paroxysmal homoglobinuria, the homoglobinuria of snake venom poisoning, incompatible blood transfusion, the homoglobinuria of crush injury, favism, and the red water fever of cattle, due to Babesia bovis. In Africans homoglobinuria also occurs in association with sickle-cell anomia.

Geographical distribution follows that of subtertian malaria—the West Coast of Africa from Senegal southwards, in the deltas of the Gambia, Niger and Congo. In East Africa on the Zambosi, the lower Shiré and shores in Lake Nyasa, in Tanganyika, Uganda, North and South Bhodesia, Abyssinia, Algeria, in South Madagascar and Mauritius.

In Asia, in Palestine, South Persia and Iraq; in India, Bihar, Assam, Darjeeling, Terai, Dooars, Merut and Amritsar; Burma, and North Siam; in China, in Yunnan, in Java, Indonesia, New Guinea and the Solomon

Islands.

In America, it used to occur in Southern States, in Central America, in Guianas, Upper Amazon, North-East Brazil, Venezuela, Jamaica, St. Kitts and Trinidad.

In Europe, Bulgaria, Macedonia, Albania, Greece, Sicily, Sardinia, Central Italy.

Epidemiology.—At times blackwater fever appeared to assume an epidemic form. Very often, as in yellow fever, the magnitude of an "epidemic" depended on the number of susceptible persons—new arrivals, it may be other than Europeans—within the endemic region; as, for instance, Bengali clerks in the Punjab, Egyptians in the Sudan, Chinese imported into British Guiana, negroes in Panama, and Central African natives from malaria-free highlands who go to live in the malarial foothills or plains. Thus it broke out among the labourers employed in making the canal through the Isthmus of Corinth.

Blackwater was comparatively rare in West African negroes, but now, since the institution of antimalaria measures and the lack of immunity

thus produced, it is as frequent in them, in Arabs and Hindoos as it was in Europeans. Reyntjens and Chesterman emphasized that, under normal conditions, the negro child, during its first year of life, escapes blackwater though it frequently dies of malaria. When, however, it is protected against the effects of malaria by quininization, it may become susceptible to blackwater.

The occurrence of several cases in the same family may not be pure coincidence, but is explained by common exposure to subtertian malaria. "Blackwater-fever houses" in Rhodesia prove on investigation to be bungalows with exceptionally bad surroundings, and highly malarious. In British Guiana the same tendency has been noted by Giglioli.

Ætiology.—Many factors formerly discussed can now be discarded.

Malaria theory.—Although blackwater fever is co-endemic with subtertian malaria in several regions, it is not so in all parts of the world. To Deeks and James in Panama must be given the credit of definitely associating the subtertian malaria parasite with blackwater fever and of successfully demonstrating that measures devised for suppressing malaria are singularly efficient in extirpating it also

The production by S. P. James of blackwater fever in paralytic subjects, artificially inoculated with certain strains of subtertian malaria, and the analogous effects brought about by massive infection of monkeys (*Macaca*) with *Plasmodium knowlesi*, appear almost conclusive that the generally-accepted ætiology is correct.

In therapeutic malaria no case of blackwater has ever been observed in association with *P. vivax*, *P. malariæ* or *P. ovale* infection, but solely with *P. falciparum*.

Ouinine and other drugs.—One stumbling-block in understanding the true mechanism of blackwater fever is the influence of quinine and sulphonamides in causing extensive hæmolysis. Both are lytic agents in vitro, but it is known that quinine in healthy persons does occasionally cause hæmoglobinuria and a clinical picture resembling blackwater. Two such cases have been reported in patients with an idiosyncrasy to quinine by Terplan and Javert (1936) and again by Vartan and Discombe (1940). Both these were women who took large doses (76 gr.) of quinine as abortifacients. Fatal hæmoglobinuria resulted, with pathological appearances of true blackwater fever. Methemoglobin was demonstrated in the urine. Neither patient had ever been exposed to malarial infection. If this is true, then it is conceivable that hæmoglobinuria may ensue in patients infected with P. vivax and P. malariæ and excessive quinine dosage. In some susceptible normal individuals quinine, in small doses, may produce a transient hæmoglobinuria, as in the instances cited by Manson, Thomson and Macmillan. But true blackwater fever occurs in native races to whom quinine is quite unknown; and, indeed, it was recognized by Hippocrates long before the introduction of cinchona bark, whilst Connal in Nigeria recorded 24 cases of severe blackwater in negroes who had never taken quinine, and demonstrated from death-rates that regular quinine takers were less liable to a fatal blackwater attack than those who took this drug in an irregular manner.

Again, Thomson in Rhodesia, has shown that certain malaria-infected individuals are specially liable to mild blackwater attacks after even small doses of quinine. Mithlens and Knabe published a case of extraordinary quinine susceptibility in a young patient from West Africa in whom less than gr. 1 quinine-urethane invariably produced blackwater. Fairley and Murgatroyd cited another instance of double infection with *P. falciparum* and *P. vivax*, where

a similar susceptibility to quinine was noted, but later, when the malaria infection had disappeared, this drug, even in large doses, had no similar action nor was there any evidence of increased sensitivity to it by cutaneous tests. Though malaria is the chief factor, any antimalarial drug can be a precipitating agent. The Editor has had this experience with atebrin, and others with paludrine.

Sensitization.—Findlay and Markson (1947), in a series of experiments on African volunteers who had recovered from blackwater, produced relapses two, three and nine days after with an intramuscular injection of 5 ml. of subtertian malaria blood.

In order to develop one attack of blackwater fever it is necessary to be sensitized to the malaria parasite and then it is possible to induce a second attack in those still sensitized by injection of a fresh dose of antigen, just as a new attack of asthma may be induced by exposure to the correct allergen.

Mechanism of hæmolysis.—This is not yet fully understood, but the following facts have been ascertained. Hæmolysis affects parasitized, as well as unparasitized, cells and this in a minor degree, is analogous to that observed in malaria, uncomplicated by hæmolylobinuria. The splenic factor is often considered a possibility in lysis, mainly on the analogy of the part it plays in other hæmolytic states. Foy and Kondi postulate that the spleen may function as a reservoir for hypothetical hæmolysins. They have injected the hæmolysing blood of blackwater into a recipient who responded, not by reproducing blackwater or any other signs of hæmolysis, but by subsequently developing subtertian malaria.

Stephens and Christophers found in an attack of blackwater the red cells showed an increased resistance to different strengths of saline. But red cells from a case of blackwater are rapidly lysed, when transfused into a normal subject, and normal cells similarly so, if injected into a blackwater patient during a lytic phase, but it is apparent that lysis is not primarily due only to changes in the red cells of the patient. An important bearing in this connection is the discovery by Maegraith, Findlay and Martin (1943) of a heat-labile lytic agent in human tissues which is inhibited by normal sera. The latter factor is reduced during the hæmolytic crisis of blackwater. It is therefore suggested that in increased hæmolysis the inhibitory factor has disturbed the balance of the lytic agent and inhibitor to the lytic side.

Foy and Kondi, during their five years' experiences in Macedonia, found a relationship between the number of malaria cases in one year and the number of cases of blackwater in an already sensitized population, but no such correlation in an unsensitized population. Liberation of hæmoglobin-hæmoglobinuria can readily be demonstrated when the blood-serum is examined directly the crisis takes place and probably, by the time the pigment appears in the urine, a large proportion of erythrocytes has already been destroyed. The pigment is removed by phagocytosis by the reticulo-endothelium and converted into bilirubin, which in turn is absorbed by the liver cells and eventually appears in the bile; therefore some degree of hyperbilirubinæmia is common in blackwater. Some excess of hæmoglobin pigment is passed in the urine as oxyhæmoglobin (red in alkaline urine) or as methæmoglobin (dark reddish-brown in acid urine), but some remains in the plasma in the form of oxy- and methæmoglobin.

Some of the hæmoglobin, converted into methæmoglobin, is then excreted in the kidney and forms the cylindrical plugs in the tubules which represent the highly albuminous hæmoglobin-containing exudate which were formerly considered to constitute the mechanical cause of anuria.

Methæmalbumin (pseudomethæmoglobin) or hæmatinalbumin (Keilin), a pigment described by Fairley and Bromfield, is brownish in colour resembling

methæmoglobin by spectroscopic analysis; it is not reduced by Stokes's reagent or by ammonium sulphide. Being a non-threshold substance it never appears in the urine. It is probably produced by union of hæmatin (ferric) in plasma with serum albumin. The pigment can be synthesized in vitro by the addition of alkaline hæmatin (ferric), prepared from pure hæmin, to human or simian plasma to 37° C. It therefore appears to be a chemical compound, consisting of a prosthetic group, oxidized hæmatin and a protein-natural serum albumin (crystal-albumin). Schumm and Hegler first demonstrated hæmatin in human serum and that it also gives a spectrum resembling that of methæmoglobin. Methæmal-buminæmia occurs during intravascular hæmolysis in many other conditions and after certain drugs, such as a combination of quinine and pamaquin. Methæmal-bumin should be regarded as a product of normal hæmolytic metabolism when free hæmoglobin is liberated in the serum, but a severe hæmolysis is necessary before it becomes apparent. It is recognized that since quinine is no longer used as a prophylactic, blackwater has practically disappeared.

Hæmatinuria has been found in a series of pathological conditions such as potassium chlorate, dinitrobenzol poisoning, as well as in hæmolytic states, such as pernicious anæmia, paroxysmal hæmoglobinuria and even malaria. In blackwater the blood urea is raised, especially in cases threatened with suppression

of urine and oliguria.

Yorke, Murgatroyd and Owen demonstrated that blood urea commonly rises in uncomplicated cases to 65 mgm. per cent. on the fourth day of the disease and there is a similar rise in severe subtertian malaria. In one of the Editor's cases 207 mgm. was recorded with ultimate recovery and even higher figures have been given by others. Other features are decrease in the plasma bicarbonate and a definite lowering of the alkali reserve in association with urea retention.

The mechanism of anuria has been the subject of some controversy and some of the older hypotheses have been called in question.

Foy, Gluckman and Kondi (1944) found that complete anuria was not associated with blockage of renal tubules. It is pointed out that methæmoglobin is an oxidation product of hæmoglobin, the iron moiety being converted from the divalent to the trivalent state, but a number of substances, not oxidizing agents, such as aniline, acetanilide, and sulphonamide also produce methæmoglobinæmia. Renal failure in blackwater, incompatible transfusions, crush injuries, uteroplacental damage and severe vomiting, as well as in sulphonamide poisoning, could not be explained simply as the result of blockage of renal tubules by products of hæmoglobin precipitated from an acid urine.

Following on this Maegraith and Findlay (1945) stated definitely that blockage of the renal tubules with debris and hæmoglobin products is not the deciding factor in the production of oliguria. The changes in the renal epithelium were

thought to be partly due to anoxia.

Finally, Maegraith and Havard (1946), on the analogy of anoxia in other different conditions, such as surgical shock, cholera, renal failure, think that, in oliguria and anuria (tubulo-vascular syndrome), kidney changes are produced by lack of oxygen, resulting from changes in the renal blood flow.

There is a reduction in total blood flow through the kidney, a redistribution of blood flow through its component parts, and, in consequence, the cortex suffers

from anæmia and anoxia, either relative or absolute.

Anuria results then from the renal anoxia syndrome and primarily from the failure of glomerular flow. On the other hand Dawson and Findlay (1947), in experiments on the relation of hæmoglobinuria and anoxia with reference to blackwater fever in dogs and monkeys, have brought forward evidence to suggest that retention of histidine may be related to renal failure and development of pressor activity in the blood, whilst in patients with hæmoglobinuria they have

demonstrated an increased exerction of histidine in the urine. It is suggested that in all cases of renal anoxia a proleolytic enzyme is liberated from the tissues and that it acts on various substances to produce polypeptides, which act as constrictors of the glomerular arteries and thus decrease the blood supply to the glomerulus.

The mechanism of other hamoglobinurias has been studied. In paroxysmal hamoglobinuria, if the blood be withdrawn and the scrum separated, then cooled to freezing-point, and subsequently warmed to 37° C, with the addition of the patient's crythrocytes, active hamolysis takes place. This does not occur in blackwater-fever cases. The test by which this fact is brought out is known as Yorke's autolytic reaction.¹

Donath and Landsteiner have shown that in this disease hamolysis takes place

in the peripheral blood, and that cold is the exciting cause.

The theoretical considerations which underlie this reaction are complicated, and concern the mechanism of immunity, and the proportion of immune body and complement. In the serum of paroxysmal hæmoglobinuria the immune body is greatly in excess of the complement, whereas in blackwater fever the reverse obtains.

Dacie, Isräels and Wilkinson have drawn attention to paroxysmal hæmoglobinuria of the Marchiafava type, the chief characteristics of which consist of chronic hæmolytic anæmia, associated with jaundice, and persistent hæmoglobinæmia. Autohæmolysis was demonstrated in vitro and shown to be dependent on the pH of the system. It has been shown that it is a nocturnal hæmoglobinuria, and that the urine is clear by day. The pigment is found to be methæmoglobin.

Favism in Greece and Sardinia is a syndrome which may be confused with blackwater fever; hæmoglobinuria develops after eating broad beans (Vicia fava) (Poy and Kondi). Similar cases have now been described in the United States, Italy, Sicily and Palestine. This is probably an allergic manifestation.

Predisposing causes.—Individuals of all ages and both sexes are liable, but from the facts already put forward it is obvious that black water occurs more frequently in European men of mature years who live in the countries where the disease is endemic. At one time race was considered an important factor. Negroes who live in places which are free from this disease develop blackwater fever as readily as Europeans, if they are exposed to the same conditions. Plehn mentioned serious outbreaks among natives on the Cameroon mountains, those who come to the coast from the interior being especially attacked.

Europeans are rarely attacked within the first year of residence in a blackwater-fever country, though cases have been reported after so short a residence as three or four months, and exceptional attacks may develop in those who have not previously shown definite symptoms of malaria. Comparable is the dramatic occurrence of blackwater fever in apparently healthy persons who have arrived in England at the expiration of their duty, or on leave. As often as not, the patient gives no previous history of fever while in residence in the tropics. The explanation seems to be that a subtertian infection is lying latent until aroused by exposure to cold, alcohol, or some other factor.

The disease observes a roughly seasonal incidence; it is specially frequent in late summer and autumn in the southern states of America. On the

 $^{^1}$ (1) Blood placed in incubator at 37° C. at once; no hamolysis. (2) Serum kept at 0° C for 5–7 mins, then in incubator for an hour with erythrocytes; hemolysis. (3) Serum kept at 0° C. for an hour, then in incubator with erythrocytes; little hemolysis.

West Coast of Africa it seems to be most prevalent at the close of the rainy season, or in August and September; in Central Africa and Nyasaland, especially in the highlands, a maximal incidence is seen during the wettest months, May to August, when the lowest temperatures are registered. In Southern Rhodesia, where the hot rainy season and the dry cold season are sharply defined, the malarial incidence increases after the rains in April; that of blackwater fever immediately rises also, and is maintained from March to July. During the 1914–18 war, in Salonika and Palestine, cases occurred among the troops especially during the cold winter months.

Pathology of Blackwater Fever.—The morbid anatomy and microscopic pathology of blackwater represent an hypertrophied picture of subtertian malaria. Certain points need emphasis. The gall-bladder is distended with dark-green bile. The *spleen* is soft, dark and contains a large amount of blood pigment and hæmozoin with evidence of hæmatophagy by macrophage cells. The *liver* is congested, dark and often shows areas of focal necrosis. The *kidneys* are large and congested and of a peculiar sandalwood or greyish-brown colour. The tubules are blocked with hæmoglobin infarcts and debris. The cells of the collecting tubules are laden with hæmofuscin, whilst the capillaries are filled with hæmozoin. The appearances resemble those seen in crush-injury, favism, snake-venom poisoning and incompatible blood transfusion. In more chronic cases the kidneys resemble those of chronic parenchymatous nephritis.

The blood changes are similar to those of acute subtertian malaria with parasitæmia. There is a great reduction of red blood corpuscles, the degree depending on the extent of hæmolysis. The count may fall to one million per c.mm. in 24 hours, but in fulminating cases half that number has been recorded. At this stage shadow corpuscles can be seen in fresh preparations and effete red

cells within the phagocytes.

During recovery there is considerable reticulocytosis with intense polychromasia, stippling of the red blood corpuscles, and sometimes there are normo- and megaloblasts. There is usually an increase of the mononuclear cells, about 12 per cent. In the earlier stages the serum contains methæmoglobin and methæmalbumin.

Symptoms.—Some clinicians recognize a clinical condition which, for want of a better term, may be described as a pre-blackwater state, indicating a suspicion that blackwater is imminent, and it is wise to be on the look-out for the following clinical signs: The patient is one who has passed through several slight attacks of fever, or at any rate has been infected with the subtertian parasite for several months. The complexion is sallow, the conjunctiva icteric, the liver enlarged, congested and tender, the tongue furred, the spleen is generally enlarged, and constipation is the rule. There is usually persistent headache. The urine is dark, owing to the excretion of increased amounts of urobilinogen, and contains a slight amount of albumin. On examining the blood, scanty ring-forms of the parasite may be found, but it is noteworthy that cases of subtertian malaria with high fever and large numbers of parasites in the peripheral blood do not, as a rule, develop blackwater.

The onset of blackwater fever is usually sudden. A slight or, more generally, a very severe rigor is followed by intermitting, remitting, or irregular fever with marked bilious symptoms. The pyrexia and rigors do not seem to be the effects of the malaria parasites as much as of a sudden liberation of the products of hæmolysis; in other words, resembling

a hæmoclasic crisis or "protein shock." Earlier or later in the attack. usually during rigor, the patient becomes conscious of aching pain-perhaps severe—in the loins, in the region of the liver and spleen, which are enlarged and palpable, and over the bladder. In exceptional instances these local pains are absent. In response to a somewhat urgent desire he passes water, when he is astonished to see that his urine has become very dark in colour, perhaps malaga-coloured, or possibly almost black. fever continues, though it is not necessarily very high. Very likely he suffers from epigastric pain and distress, bilious vomiting to an unusual extent and, it may be, bilious diarrhea; or he may be constipated. The pain in the loins and the liver-ache continue, and the urine becomes darker and darker. By and by he breaks into a profuse sweat, and the fever gradually subsides. The urine, which hitherto may have been somewhat scanty, now flows freely; and after passing through various paling shades. from dark brown to sherry red, becomes natural. Usually, and coincidently with the appearance of the dark colour in the urine, or even before this, the skin and scleræ rapidly acquire a deep saffron-yellow tint. This icteric condition persists, and even deepens, during the progress of the fever, continuing to be a striking feature for several days. When the fever subsides the patient is conscious of a feeling of intense weakness. from which he recovers but slowly. Fever, with or without rigor, may recur next day, or for several days; or it may cease; or it may be remittent, or almost continued, in type. The hæmoglobinuria may recur with each rise of temperature, or there may be only one or two outbursts; it may continue for an hour or two only; or it may persist off and on for several days or even weeks.

In the more severe form of blackwater there is usually a very great amount of bilious vomiting, of intense epigastric distress, and of severe liver- and loin- ache. The urine may continue copious and very dark; or, continuing hæmoglobinous, it may gradually get more and more scanty, acquiring a gummy consistency, a few drops only being passed at a time. It is considered that the kidneys may excrete up to 36 per cent. of the total hæmoglobin in the blood, though this by no means represents the total amount liberated in many cases. Finally, urinary excretion may be completely suppressed.

In severe cases death is the rule. It appears to be brought about in one of three or four ways. The fever may assume the typho-adynamic type; or sudden cerebral, hyperpyrexial, or algid symptoms may supervene. Hiccup is a fatal sign. In other cases the symptoms may be like those consequent on sudden and profuse hæmorrhage—jactitation, sweating, sighing, syncope. Death may take place from sudden heartfailure after slight exertion, or from exhaustion consequent upon cyclical vomiting, or from sudden hæmorrhage from stomach or bowel. Or it may be that suppression of urine, persisting for several days, terminates, as cases of suppression usually do, in sudden syncope, or convulsions and coma. In very acute cases death may be due to focal necrosis of the liver. More rarely nephritis may ensue and the patient die from uræmia three or four weeks after all signs of hæmoglobinuria and fever have disappeared, or he may succumb to some superimposed infection,

streptococcal, septicæmic, or pneumonic. One attack of blackwater appears to predispose the individual to a second, and second attacks, or more than two, have been noted in Nigeria in about 20 per cent. of cases; according to Stephens, sixteen is the largest number recorded. It is necessary to lay special stress on these points, for when a man has suffered and recovered from two attacks, the third is generally fatal.

Blackwater fever is highly dangerous to pregnant women, during parturition or during the puerperium. Particular care should always be taken to guard them from malaria in these circumstances, especially in districts in which the subtertian parasite is most prevalent. Their blood should be frequently examined and they should take prophylactic courses of paludrine or atebrin from time to time. Thomas and Miller relate a remarkable case of blackwater during pregnancy at the thirtieth week with delivery of a dead feetus in the middle of the attack. The patient's life was saved by repeated blood and drip transfusions, and the case was still further complicated by a severe attack of Bact. coli pyelitis. Foy and Kondi have examined a premature feetus born of a woman who died of blackwater fever. No trace of methæmoglobin, malaria parasites, or pigment was found in the blood, though the maternal placental spaces were crowded with schizonts of P. falciparum.

Sequelæ.—Anæmia and debility are the common sequels of a blackwaterfever attack, but usually, under hygienic conditions, the recovery is astoundingly rapid. A curious sequel is cholelithiasis, owing to the formation of pigmented biliary calculi from inspissation of bile in the gallbladder. K. D. Fairley originally drew attention to this phenomenon in a case in Australia, and the Editor has since seen two cases in which this was noted three weeks after the cessation of blackwater, and pigmented

calculi were demonstrated at operation.

Generally the hæmolysis of blackwater destroys all the parasites circulating in the blood, but occasionally some may escape and produce attacks of fever during convalescence. Exceptionally they may be found in the bloodstream during the blackwater attack and then are apt to coincide with recrudescence of hæmolysis.

The urine.—If the characteristic dark-brown, generally acid, urine of a hæmoglobinuric case be stood for some time in a urine glass, it will separate into two well-marked layers; an upper of a clear, though very dark, port-wine tint, and a lower—perhaps amounting to one-half or one-third of the entire bulk-of a somewhat brownish-grey sediment in which an enormous number of hyaline and hæmoglobin tube-casts are found, together with a large quantity of brownish granular material. Epithelium is also found. Blood-corpuscles may be entirely absent, or few. With the hæmoglobin there is also an escape of the serum albumin of the blood, for the urine, in many cases, turns almost solid on boiling. The precipitated albumin carries down with it, as it subsides, the dissolved and suspended hæmoglobin, leaving a pale-yellow supernatant urine. some days after the urine has regained a normal appearance it will still contain albumin, though in gradually diminishing amount. Spectroscopic examination gives the characteristic bands of oxyhæmoglobin, as well as those of methæmoglobin. The appearance of oxyhæmoglobin is usual in very severe or fatal cases, methemoglobin in the less severe or mild, in which the prognosis is more favourable. After the disappearance of the blood-pigments, urobilinogen may be demonstrated in pathological amounts and sometimes bilirubin.

Eye complications.—Hæmorrhages into the retina sometimes occur during the course of blackwater, and the Editor has seen one case of altitudinal hemianopia where there was total blindness in the lower half of the visual field.

Diagnosis.—The history of the patient, the attendant rigor, the hæmolytic icterus and hæmoglobinuria usually suffice.

Differential diagnosis has to be made from paroxysmal hemoglobinuria, bilious remittent subtertian malaria, snake-poisoning, favism, yellow fever and leptospirosis. If it be borne in mind that rigor, hemoglobinuria, icterus and pyrexia are all in evidence at the outset in blackwater and that it is acquired only in certain hyperendemic malarious centres, an error in diagnosis is impossible.

Treatment.—Patients who are suffering from or are threatened with hæmoglobinuria, who are in the pre-blackwater state (p. 65), or who have had this disease before should, on the slightest indication of fever, go to bed at once, keep the skin warm and scrupulously protected from draughts, and take plenty of warm fluid. If parasites are present in the blood (usually P. falciparum, though there may be superinfection with P. vivax, P. malarice or P. ovale), the patient should be treated with full doses of paludrine or chloroguine. Patients threatened with blackwater fever should not travel; should it become imperative for any reason to move them, an injection of morphia should be given, or they may be kept under slight chloroform anæsthesia during the worst part of the journey. Injections of sodium luminal (phenobarbitonum solubile B.P., 10 gr., and a further 5 gr. two hours later) are said to keep patients quiet for two days. Glucose, in large quantities by mouth and intravenously in 5 per cent. solution, is indicated, as it has been shown by Kubo and Kondo that it may prevent hæmolysis of red corpuscles. It has hitherto been held that suppression of urine is less likely to take place when the urine is alkaline, that therefore massive doses of sodium citrate and bicarbonate are indicated, but Maegraith and others insist, on physiological grounds, that such intensive alkali treatment may be dangerous and at least should be controlled by estimation of the alkali reserve. In reasonable doses (20-30 gr. in 24 hours), these salts may produce diuresis, but acidosis is very uncommon.

Replacement of fluid and salt is necessary. Both may be lost by the patient by vomiting, diarrhœa or sweating. As far as possible fluid intake should be estimated and balanced against output, but it is a serious mistake to push fluids too vigorously. Should vomiting and coma prevent fluids being taken by the mouth, intravenous injections of physiological saline by the drip method are indicated. In coma or in convulsions drip transfusion with 5 per cent. glucose in saline should be given, but large quantities—eight or more pints may be necessary. Marked restlessness should be controlled by injections of morphia.

In threatened anuria hot fomentations may be applied to the loins and high rectal lavage with hot water appear to exert a diuretic effect. Physiological saline solution 6–8 ozs. at 100° F. should be injected into the rectum at intervals of half an hour.

Lavage of the kidney pelvis by ureteric catheters has been practised by Ross in Southern Rhodesia with success. After inserting the catheter 4 ml. of warm sterile saline were injected by means of a syringe and repeated withdrawals effected twelve times.

Blood transfusions.—If the red cell count is one and a half millions or less, or the carriage of oxygen to the vital tissues is reduced, transfusions are absolutely necessary. As citrated blood is liable to give severe reactions, injection of concentrated red cells is the best method, if facilities are available. It is most necessary, on account of autoagglutination, to perform cross-matching of the donor's corpuscles with the 'patient's serum and vice versa. Repeated transfusions can be employed and as much as 500 ml. given on each occasion. There is no evidence that it arrests hæmolysis, but it is distinctly a life-saving measure. Wherever possible the drip transfusion method should be adopted. With replacement of active-functioning cells urinary excretion is often re-established and the blood urea falls to normal levels. As the excretion of ascorbic acid is increased in subtertian malaria and blackwater, this vitamin should be supplied in full doses during the convalescent stages. Potent proteolysed liver extracts by injection certainly help to restore hæmopoiesis and possibly folic acid (folvite) may also be useful. Linley-Adams (1953) has reported in one critical case the favourable action of cortisone (150 mgm.) by intramuscular injection.

It is advisable to give paludrine throughout the blackwater attack with the idea of preventing any possible relapse of malaria and to forestall any further hæmolysis. There may be, moreover, a superadded infection with *P. vivax*, *P. ovale* or *P. malaria*, and cases are recorded in which one or other of those parasites have been demonstrated in the blood during convalescence. They should be regarded as concomitants, not as the exciting cause of blackwater.

Nursing is most important in the management of blackwater fever. If the stomach will retain food, this should be given in a bland and fluid form, but there should be no attempt at forcible feeding, especially with rich and indigestible viands. One precaution against syncope must be sedulously enforced: the patient must not be allowed to sit up, much less to get out of bed, until food has been retained and assimilated, and the risk of sudden death has passed. The foot of the bed should be raised on blocks.

Usually a severe attack of blackwater fever extirpates the associated malaria infection; but this is not always so, and a relapse of fever with parasitæmia is by no means uncommon. To guard against it, an aftercourse of atebrin or paludrine treatment is always advisable.

If possible, the subject of blackwater fever should quit the endemic area, and never return to it or to any malarial locality; a severe attack,

¹ Plasmoquine (pamaquine), p. 87, is liable to provoke blackwater in acute subtertian malaria and therefore should not be used.

or a second attack, implying special susceptibility, should be regarded as a definite indication to leave the area. It should be remembered that blackwater patients are specially liable to retinal homorrhage and may also develop pigmented gallstones. In their enfeebled state they are also liable to secondary infections, such as pneumonia, streptococcal septicemia and cardiac irregularities. A third attack is often fatal, though there are exceptional instances of seasoned individuals in West Africa who have survived as many as ten.

Mortality of blackwater.—This varies greatly in the same and in different places, and under the same treatment. Some cases are so mild and transient, amounting, perhaps, to a single emission of hæmoglobinous urine, with little or no fever, that they are unattended with risk; on the other hand, a practitioner may encounter a run of severe cases which nearly all die. According to modern teaching the chances of survival depend upon the number of nephrons in the kidney which have escaped destruction as the result of renal anoxia. Some old residents in Africa have passed through ten or more attacks with impunity. In Southern Nigeria and in Algeria the case-mortality has been as high as 50 per cent., but, as a general average, it may be put down as about 25 per cent.

Prophylaxis.—The prophylaxis of blackwater fever is obviously identical with that of malaria.

Findlay (1949) has put this shortly as follows: from 1941-1945 in military personnel in W. Africa there was increased efficiency in malaria control. The number of malaria cases and the incidence of blackwater fever per 1,000 cases were: 1941, 5,820 (6.76); 1942, 8,884 (11.54); 1948, 4,489 (8.68); 1944, 2,319 (0.85); 1945, 568 (0). In March, 1948, mepacrine (atebrin) was substituted for quinine as a suppressive. Thereafter there were only 19 cases of blackwater fever in Europeans. It was concluded that mepacrine protected the European against blackwater fever during 1944–1945.

Other sequelæ of malaria.—The term malarial cachexia is applied to a group of conditions, more or less chronic, believed to be the result of an antecedent attack of severe malarial fever, or of a succession of such

attacks, or of prolonged exposure to malarial influences.

The leading symptoms are those of anæmia, characterized by peculiar sallowness of the skin, yellow sclerotics, enlargement of the spleen and, it may be, of the liver. As a rule, the subjects of cachexia are liable to frequent and irregular attacks of fever, though in highly malarious countries it is not unusual to see cases in which fever has never been a feature, or it may have been very mild. In such countries a large proportion of the population have enormously enlarged spleens, causing great protrusion of the abdomen, together with much emaciation and dry, rough skins. It is said that in some intensely malarial countries children are occasionally born with enlarged spleens; in some instances they are infected through the mother in utero, but it is probable that in most cases they become inoculated with parasites immediately after birth.

In the young the general growth of the body is stunted, and puberty retarded. Abortion and sterility are common effects of malarial cachexia

in adults.

Cardiac changes in malaria.—Choked capillaries cause injury to endothelium and absorption of malaria toxins with malnutrition of muscular tissue and multiple small necroses. Permanent injury may ensue, and the electrocardiogram may disclose dilatation, extrasystoles and irregular action of the auricles.

The spleen may become so enlarged under repeated attacks of the congestion attending a succession of fever fits, or in consequence of a less active and perhaps feverless hæmolysis, that it may come to weigh many pounds, and occupy a large part of the abdominal cavity.

Estimation of malarial prevalence.—The relative absence or prevalence of these enlarged spleens or "ague cakes" in the native population is a rough indication of the malarial risk in any particular district. Wherever they are common the district is malarious, and therefore unhealthy, perhaps to Europeans deadly, and should be looked upon as extremely unfavourable for camping or residential purposes.

Another practical point is that these enlarged spleens are easily ruptured by a blow on the belly; this fact must be remembered in administering even mild corporal punishment to natives of malarious countries. Splenic ruptures are, of course, generally fatal, unless immediately operated on. Occasionally, the spleen may rupture spontaneously, owing to rapid increase in size in the course of an attack of fever; but splenectomy does not necessarily eradicate the malarial infection.

Six cases of ruptured spleen were operated upon in the recent East African campaign. After splenectomy, intravenous transfusion of blood from the peritoneal cavity is an easy and efficacious treatment. The blood is collected, strained through sterile gauze, citrated and given in the usual manner (Erasmus).

Splenic rate or index.—In estimating the amount of malaria in a community the splenic index has been found to be most reliable. Children between the ages of two and ten form the only safe guide (Stephens and Christophers), for among the inhabitants of a very malarious country the adults are more or less immune and their spleens are diminished in proportion. The infantile spleen rate per cent. is the basis of the endemic malariousness of a locality, though it is necessary to guard against a tendency to over-estimate its value. Barber, in the Philippines, working with children 5–10 years of age, obtained a splenic index of 13-3 and a parasite index of 11.

It is difficult by any known method to detect changes in the spleen unless they are of some magnitude. Some authorities consider that a spleen must be twice its normal size before it can be felt. The degree of splenic enlargement may be measured with the child standing up or lying down. Considerable differences in the results obtained are given by the two methods, higher values being obtained in the recumbent position. In India and in the tropics generally, where gross degrees of enlargement are commonly encountered, the standing position is nearly always used. The best method is for the child to be drawn gently across the observer's knee, the hand being inserted beneath the scanty clothing and pressed against the costal margin while the child is told to take a deep breath. The degree of splenic enlargement is usually classified in finger-breadths below the costal margin. Obviously this method is liable to fallacies. The distance from the costal arch to the pubes is very different in an infant of two years and a child of

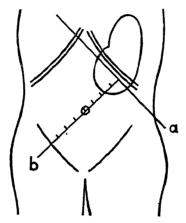


Fig. 6.—Schüffner's method of determining degree of splenic enlargement.
(a) denotes the upper limit along the left costal margin; (b) a line drawn at right angles through the tip of the spleen and the umbilicus.

ten. Christophers devised a method by applying to the actual measurement (costal margin to apex of enlarged spleen) a correction based upon the nipple-umbilicus length of the child.

In the average Indian child of six years of age the four-finger spleen reaches to the level of the umbilicus. In malaria surveys, the following classification is generally adopted:

Spleen-rate greater than 50 per cent. — Hyperendemic. Spleen-rate 25 per cent. to 50 per cent. — Highly endemic. Spleen-rate 10 per cent. to 25 per cent. — Moderately endemic. Spleen-rate less than 10 per cent. — Healthy.

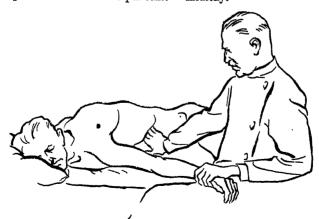


Fig. 7.—Method of spleen palpation. (After Schotter; Munch. Med. Wochenschr.)

The child spleen-rate gives the measure of endemicity, the average enlargement that of intensity.

Schüffner's method of estimating splenic enlargement has many advocates: a line is drawn along the left costal margin and a second at right angles to it passing through the apex of the spleen and the umbilicus (Fig. 6). The latter is divided into eight sections and the degree of splenic enlargement is assessed accordingly.

Occasionally an enlarged spleen has to be differentiated from an enlarged left kidney containing a cyst or a hypernephroma; this has usually a rounded lower pole and a smooth round margin. An area of resonance can be elicited on its anterior surface, caused by the resonant band of the descending colon. The urine contains albumin and casts. Considerable care is sometimes necessary in the accurate palpation of the spleen. This is best done by using the radial aspect of the right index finger with the patient recumbent on his right side and the abdomen relaxed, and the left arm extended (Fig. 7). Most authorities maintain that the greatest degree of splenomegaly occurs in *P. vivax* infections, but that in *P. falciparum* there is a higher proportion of smaller spleens.

Although the chronic fibrous spleen remains quiescent and does not interfere with general health, yet it may occasionally assume an active pathogenic role. Fairley has described a hæmolytic hypochromic anæmia associated with postmalarial splenomegaly of the Banti type in which splenectomy was followed by a hæmolytic megalocytic erythroblastic anæmia.

The parasite-rate or index is a simple percentage figure calculated from the number of persons actually showing parasites in the peripheral blood at the time of examination. Figures for children and adults should be kept separate, as the spleen-rate falls with age more rapidly than does the parasite-rate, which shows how many adults of a community are really "healthy carriers."

The endenic index includes all those who show either parasites or

splenomegaly.

The parasite-rate can be obtained from the study of thick as well as thin films. Curves prepared from splenic and parasite *indices* according to age run parallel to a remarkable degree. The parasite index as a sign of infectivity is more reliable up to five years of age, after which to the age of twenty-five it is on an average 10 per cent. less reliable than the splenic index.

Wilson and Clark, in a survey of 1,100 Haitian labourers and 2,007 school-children between 6 and 14 years of age, found that the parasite rate, determined by the thick-film method, was of far greater value in estimating the prevalence of malaria than was the splenic index. Of 11,000 adults 23.5 per cent. had positive blood-films and 3.03 per cent. had palpable spleens: of 2,007 children, 50.52 per cent. had positive blood-films and 3.03 per cent. palpable spleens.

In many areas malaria transmission varies greatly according to the season of the year, mosquitoes usually (but not always) being most prevalent during and after the rains. Spleen and parasite rates observed during heavy transmission periods are likely to be much higher than at other seasons, and, in estimating endemicity, account must be taken of these factors. In general, a reliable estimate cannot be made, unless rates are taken over at least one year, and even then that particular year may be

abnormal. Where transmission continues throughout the year the average rates are more reliable.

Liver and gall bladder.—Chronic hepatomegaly is a not infrequent sequel of malaria, and hepatic congestion may gradually become more or less permanent. Siderosis is produced from chemical changes in the liver undergone by hæmosiderin. Together with this there may be chronic engorgement of the gall-bladder, which predisposes to cholecystitis and cholelithiasis. It is small wonder that with such a polycholia pigmented calculi are apt to form. For instance Vauthey has recorded 28 cases of biliary colic during an attack, and 71 in which biliary attacks occurred subsequently.

Mental changes.—Loss of memory and mental impairment are frequent sequels of acute subtertian malaria, more especially of the cerebral forms. Schizophrenia has been recorded and also, occasionally, confusional insanity.

IMMUNITY IN MALARIA

In the course of malarial infection a certain degree of tolerance may develop.

In heavily-infected endemic districts, malaria is specially likely to appear in small children, and of these a proportion die early, while others acquire a degree of immunity through repeated re-infections. It has often been remarked that dark-skinned children with enormous spleens and a rich stock of malaria parasites in their blood run about fever-free, and apparently robust, but they have usually at some time passed through a few years of miserable ill-health. As these children grow up, their immunity becomes stronger and, after twenty years of age, they may remain quite free from clinical signs, and even splenic enlargement may disappear.

It is generally accepted that malaria, like other protozoal diseases, differs from bacterial infections in that the causative parasites do not disappear, but remain in the body, where a balance is established between the resistance of the organisms and the inherent tendency of the parasites to increase. Sergent, Parrot and Donatien have coined the term "premunition" to characterize the balance between immunity and re-infection. This equilibrium-tolerance of the parasites by the host should be compared with allergic conditions of symptomless latency in tuberculosis and syphilis.

Taliaferro and his associates have assigned an important rôle to the reticulo-endothelium and a similar condition has been found by Cannon and Taliaferro in birds infected with avian plasmodia. Ziemann and others endeavoured to distinguish between immunity to the toxins and that due to the parasites. In the latter case the organisms disappear gradually from the body.

Taliaferro and Mulligan attribute a considerable rôle to the macrophage cells. The reticular cells of the spleen and bone marrow rapidly become converted into the phagocytic phase and may play an essential part in the local defence of these organs

local defence of these organs.

It is well known that the negro in Africa, although he does get fever, does not get it so frequently or so severely as does the European, although the latter is

less exposed to infection. Indeed, malaria in natives is so often asymptomatic as to give the impression of quite a different disease. Amongst the Malays Schüffner observed an immunity to malaria parasites, as described by Ziemann. Of the young children, 38 per cent. were parasite carriers, while in the older ones it was as high as 50 per cent. The parasite index in adults was 8-11 per cent., and of those examined, 92 per cent. showed enlargement of the spleen. Christophers (1924) found the same conditions in India. In most districts in the tropics all three classical forms of the malaria parasite occur, and therefore immunity may be produced against all three. In an untreated population, it is found that among children benign tertian parasites disappear most quickly, quartan parasites next and subtertian persist the longest. This is also the case among adults in whom the ring forms of the latter parasite predominate while crescents are very scanty. Thus natural immunity in native populations is the result of natural selection, but each species of malaria parasite appears to be composed of different immunological strains. Thus, natives immune to strains of P. falciparum of their own districts may be subject to attacks of subtertian malaria after moving to other areas as a result of infections with new strains.

Sinton, who has given considerable attention to this aspect of immunity, believes that there are two methods of attack upon the malaria parasite and its toxins, viz. (a) cellular, and (b) humoral, and that these two factors are closely associated and act in combination.

The cellular factor is definitely established in the destruction of malaria parasites by macrophage cells. Primarily, the host reacts to the infection by an increase in the number of these cells; later, an active *specific* phagocytosis comes into being.

That the immunity produced by previous infection with an homologous strain of $P.\ vivax$ is complete has been shown recently by Shortt & Garnham in an experimentally produced human infection. It would seem that in such an immune individual the E.E. forms in the liver, which result from a fresh and overwhelming infection, are engulfed by invading leucocytes and destroyed to such an extent that no fever results.

The humoral factors are much less certain; in acquired immunity there is certainly development of specific antibodies and these are probably produced by the macrophage system as the result of stimulation of ingested parasites, acting as a specific antigen. The element concerned may be a lysin, or possibly an opsonin. Antitoxic substances are also probably produced, and there is some evidence to show that a certain degree of passive immunity can be transferred by the injection of serum from an immune subject. Macdonald has even asserted that the existence of group immunity makes control in some cases undesirable.

J. G. Thomson estimated that the process of acquiring tolerance to malaria demands continuous exposure for about fifteen years. Experiments by James and others with induced malaria seem to indicate that a certain degree of immunity can be acquired through hyper-infection, but that the immunity is not entirely specific, even for a certain species, but only for a certain strain of parasite. Bagster Wilson has suggested that in non-immunes the subtertian parasite is monomorphic, characterized by minute rings and multiple cell-infection, whilst in immune persons the parasites tend to be larger and polymorphic.

Considerations such as these explain the sudden and severe outbreaks of malaria in endemic districts. Sometimes meteorological causes combine to render conditions more favourable for the development of the transmitting anopheles with consequent increase and spread of the disease,

as in the Ceylon epidemic of 1984. Macdonald considers that in the first two years of life in hyperendemic areas, and perhaps for longer periods, in places of low endemicity, superinfection can be considered as a normal happening.

The maximum adjustment of the parasite to its host is attained when the former is able to survive without detriment to the latter. This state is what is known as fully developed premunition, the best example

of which is found in piroplasmosis of cattle in U.S.A.

Again, mass immigration from malaria-free districts may cause an outbreak of the disease, as in the Panama Canal, and in the many outbreaks during the 1914–18 war. Subsequently the Greeks repatriated from Asia Minor suffered from serious epidemics with a high mortality in malarious endemic areas in Greece. The widespread malaria epidemic in Russia in 1920 could be traced, for the most part, to migrations of a half-starved population.

The question of immunity is very much bound up with the complicated and difficult problem of nutrition. This in turn depends upon agricultural

developments and the "bonification" of the land.

DIAGNOSIS OF THE FOUR CLINICAL VARIETIES OF MALARIA

The recognition of the various forms of malaria parasite in the peripheral blood entails a knowledge of blood examination. For the details of this and of the methods of staining blood the reader is referred to the Appendix, p. 1076. Most workers prefer the thick-drop method as offering a more certain chance of discovering the parasites when scanty in the peripheral blood, but it is by no means such a certain method of distinguishing the species, and requires considerable experience in order to do so.

Effect of quinine, atebrin and other drugs on microscopical diagnosis.—It is of little use to examine the blood for the intracorpuscular forms of the malaria parasite after full doses of quinine, atebrin or paludrine, as these drugs rapidly bring about the disappearance of this phase of the parasite. The crescent, or gametocyte, of the subtertian parasite alone is unaffected by quinine or atebrin, and in suitable cases may be demonstrated for weeks after the patient is einchonized; on the other hand, plasmoquine has a selective action (see p. 87). Changes in the red blood-corpuscles, such as basophilic stippling, are sometimes of assistance, and definite increase of large mononuclear cells above 15 per cent. is suggestive. A reticulocyte crisis occurs 4–7 days after the exhibition of quinine or atebrin.

Concentration of parasites in the blood.—Rogers has devised a method of concentrating the malaria parasites in thin films. The blood is run into capillary tubes. The ends are sealed and they are centrifuged at 2,000–3,000 r.p.m. for 20–30 minutes. A scratch is made with glass-cutter about $\frac{1}{8}$ in. above the top of the packed cells. The tube held horizontally is broken at this mark. A second cut is made $\frac{1}{8}$ in. below the top of the red-cell layer and the tube broken off at the second mark. The blunt end of a Pasteur pipette is heated in a flame and bent into an

"S" shape, and the capillary tube is dropped into the pipette with serum uppermost. The tube is centrifuged and the thinned end of the pipette cut off, and with a teat applied to the butt, the blood is blown out on to a slide, films made and stained in the ordinary way.

Complement fixation.—This method of ensuring an accurate diagnosis in chronic cases was originally suggested by Gordon Thomson and considerable attention has been paid to it. As antigen an emulsion of an organ rich in parasites,

as well as artificial cultures of plasmodia, have been employed.

Coggeshall (1941) described his special method with an antigen prepared from red cells infected with *Plasmodium knowlesi*. This reaction is uninfluenced by the presence of luctic complement-fixing antibodies in induced therapeutic malaria. The test becomes positive about the second week and persists for some five months. Experimental studies suggest that this test may have considerable merit in *P. vivax* and *P. falciparum* infections. The parasitized red cells are washed free from serum and preserved by freezing and drying. The stored antigen is rehydrated and diluted 1:100 in normal saline. The supernatant fluid is used. The tests are carried out as for the standard Wassermann reaction. Dulaney, Stratman-Thomas and Warr (1942) found that 81.6 per cent. of malaria sera gave a positive reaction. Dulaney (1945) finds this method by far the most sensitive method of assessing clinical cure.

Wassermann reaction.—About 28 per cent. of malarial bloods in the acute stages of malaria, when parasites are plentiful in the peripheral blood, give a positive Wassermann reaction; but this is not so in either the chronic or quiescent stages. This fact has to be borne in mind in excluding syphilis in a malaria-infected subject.

Saunders and Turner (1935) believed that these results are not specific, but that malaria in the acute stage gives rise to anti-complementary reactions. The latest work by Kitchen, Webb and Kupper supports this view. They inoculated 30 persons with *P. vivax* and *P. falciparum* and tested the blood at intervals with the Wassermann and Kahn reactions. They obtained positive tests in every case in which malaria developed clinically; 72 per cent. of positive reactions appeared during the third and fourth weeks after inoculation of malaria, and these remained positive for more than three weeks in 60 per cent. The highest percentage of positives occurred from fifteen to twenty-one days after the last paroxysm.

Try tested 246 malaria patients, the blood being taken when the temperature was normal: 11.78 per cent. gave a positive Wassermann reaction. Of 97 with subtertian malaria, 8.2 per cent.; of 110 with benign tertian, 11.8 per cent.; of 39 with quartan malaria, 20.5 per cent. were positive. Potter (1945) found in case of *P. vivax* that all serum reactions returned to normal within 30 days.

Henry's sero-flocculation test (M.S.R.).—From examination of two pigments derived from hæmoglobin—hæmosiderin and hæmozoin—it was considered probable that they would produce in the blood antibodies of diagnostic importance for a flocculation test. Accordingly the ferro-flocculation and melano-flocculation tests were elaborated by employing melanin from ox-eyes. It has, however, become increasingly clear, as has already been suggested, that this reaction is non-specific and depends upon an increase of the euglobulin in the serum and diminution of cholesterin serum-albumin (Benhamou and Gille). Zipf finds that the malaria-serum reaction is simply a sensitive index of liability in distilled water of malaria serum. The M.S.R. is rather an indication of the behaviour of the body defence mechanism than as an index of diagnosis.

An intradermal test with antigen made from P. gallinaceum is claimed by

Makari to give satisfactory results.

Diagnosis by sternal puncture.—Schretzenmayr (1939) claimed that sternal puncture is a simple procedure, and that it should be adopted as a routine diagnostic measure; he found parasites by this method in 19 cases although blood films were negative. Aitken, Rumball and others (1943) have used this method during the recent war. They found it valuable in atypical cases, where routine examination of the peripheral blood was negative, especially in subtertian infections. A sternal puncture needle is unnecessary, and a stout truncated lumbar puncture needle can be used. It is inserted vertically through the centre of the sternum at the level of the second intercostal space and pressed firmly through the cortex. Resistance decreases when the marrow is entered. Thick drop preparations can be made, and the fluid contains more parasites than the peripheral blood. Of 294 cases of obscure illness, 256 were diagnosed by blood films, the remaining 38 by sternal puncture. Many of the latter had previously been treated as sandfly fever or neurasthenia.

Diagnosis by splenic puncture.—Spleen puncture may occasionally be used as a method of diagnosis, especially in chronic and relapsing cases due to *P. rivax*. In films, malaria pigment, free and endocorpuscular, and remains of malaria parasites may be observed, but Foy and Kondi in Macedonia found this method very disappointing.

Diagnosis of malaria by the therapeutic action of drugs.—It is unfortunately true that, where malaria exists, any case of fever is diagnosed as malaria, and the practitioner may be called in only when a considerable amount of quinine or other antimalarials had been taken and has failed to achieve the desired result. Unfortunately, too, a good many practitioners are in the habit of relying unduly upon the therapeutic action of these drugs without verifying their diagnosis by microscopic examination.

Diagnosis from clinical signs.—The most important clinical sign is periodicity of the fever, which occurs in its most typical form in the tertian and quartan infections; in the subtertian, however, fever may be most irregular, or there may be no pyrexia at all.

Enlargement of the spleen is a common clinical sign in all forms of malaria. In old-standing infections it may be very large indeed, and occupy the greater part of the abdominal cavity, but in early, and it may be very severe, cases it may not be sensibly enlarged at all, and therefore fails entirely as a clinical guide; usually, however, in the absence of splenic enlargement, splenic pain is present during the attack. Moreover, the patient may be suffering from some totally different disease, and the palpable spleen may be the result of a long-standing malaria infection. quite unconnected with the attack in question.

To the clinician accustomed to many cases, the general appearance of malaria patients, the bright glistening eye, set in rather a dusky orbit, contrasted with the pale and ochreous complexion, combine to create an almost diagnostic appearance. Amber coloured urine due to excessive urobilinuria, especially in subtertian malaria, and even in the absence of parasites in the peripheral blood, may be suggestive.

Diagnosis by the history.—Sudden fever in a previously healthy person who has recently arrived from a malarious country usually turns out to be malaria. The patient will generally give a history of similar attacks while resident abroad, but there are exceptions to this rule, for,

occasionally, residents of tropical countries may develop their first attack of malaria shortly after arriving in a cold climate, and this attack, aggravated by the conditions, may run a very severe course; this is especially the case with recent arrivals from the West Coast of Africa, and it is true for both benign tertian and subtertian infections, the parasite lying dormant in the blood-stream, perhaps as long as eight months; in the benign form a year or more.

An actual description of the febrile attack itself may be suggestive. The rapid rise of temperature, the history of the cold, the hot, and the sweating stages, the rapid defervescence of the fever, and the subsequent sense of well-being, are more characteristic of a malarial attack than of any other febrile disease. At times periodicity is a trustworthy enough clinical test. Tertian and quartan periodicity usually occur only in malarial disease, but have been seen in meningococcal septicæmia.

DIFFERENTIAL DIAGNOSIS OF MALARIA AND OF BLACKWATER FEVER

The differential diagnosis of malaria entails a knowledge of all fevers, both tropical and non-tropical. In hepatic abscess, although the liver is enlarged, the spleen is not necessarily so, and the fever occurs generally, though not invariably, in the late afternoon or evening.

In bilious remittent malaria the ieteric tinting of the skin is an early feature; albuminuria is not so common or so marked as in yellow fever.

Without the microscope it is sometimes impossible to differentiate typhoid types of malarial fever from enteric in the early stages.

The following, also, are often mistaken for malarial fever: cerebro-spinal meningitis; fever of urinary origin (sometimes renal calculus); the fever attending the passage of gall-stones, or inflammation of the gall-bladder; that associated with pyelitis and surgical kidney; perineal abscess; lymphangitis, particularly that form associated with elephantiasis and other filarial diseases; undulant fever; relapsing fever; trypanosomiasis; kala-azar; the fever associated with tuberculous disease, with ulcerative endocarditis, with some types of pernicious anæmia, with splenic leucocythæmia, with visceral syphilis, with pulmonary carcinoma, with rapidly growing sarcoma, with forms of hysteria, and with many obscure and ill-defined conditions.

Primary atypical pneumonia in its initial stages may resemble a malarial attack, and its recognition gave rise to difficulties in the Middle East campaign. Campbell (1943) described two clinical groups. The first consisted of patients who had both malaria and pneumonia, the second of those admitted with malaria who later developed pneumonia. The routine use of X-rays is indispensable; it reveals the typical mottling of the lung bases.

Priest, Kilham, Javett and Sacks found that meningococcal septicæmia may produce tertian, or even quartan, periodicity somewhat resembling that of the corresponding forms of malaria. The Editor (1941) diagnosed one such patient, with recurrent attacks of fever, who had been regarded and treated as malaria for nearly one year. Splenic pain may also be present. Erythema nodosum is sometimes seen.

Differential diagnosis of special forms of subtertian malaria.—There is a natural tendency for medical men, unacquainted with the clinical forms of subtertian malaria, to diagnose its various symptoms as manifestations of some other disease. Even surgical conditions, such, for example, as appendicitis, intestinal obstruction, or other acute abdominal disorders calling for urgent

operative interference, may be suspected. The following statement is based upon actual diagnoses which have been made on clinical grounds alone, without the confirmation of a microscopic examination, but which subsequently proved to be cases of subtertian malaria:

(a) Cerebral forms of subtertian malaria are apt to be mistaken for heatstroke. mental derangement, hysteria, alcoholism, aphasia, convulsions, epilepsy.

cerebro-spinal meningitis, or plague.

(b) Abdominal forms for dysentery, both amoebic and bacillary, cholera. intestinal obstruction, appendicitis. biliary colic, choleevstitis. hæmorrhagic pancreatitis, or liver abscess. Malarial appendicitis can be distinguished on clinical grounds by overcoming the muscular defence by patient palpation, from the subsequent passage of faces and flatus. the dicrotic, full pulse, flushed facies, and the rapid fall in temperature after a profuse sweat.

(c) Pulmonary forms-i.e., malarial pyrexia with pulmonary congestion and mvocarditis-for bronchitis, pneumonia, and pleurisy, especially on the left side (due to congestion of spleen), disordered action of the heart or

valvular disease.

(d) Those with cutaneous petechiæ for measles, endocarditis, or purpura.

(e) Febrile cases with remittent pyrexia for influenza, rheumatic fever, enteric. phlebotomus fever, trench fever, paratyphoid, or relapsing fever.

(f) Icteric cases for yellow fever, Weil's disease (leptospirosis) or infective

hepatitis.

(g) Cachectic cases for acute nephritis, pernicious anamia, spleno-medullary leucocythæmia. debility, or pulmonary tuberculosis.

(h) Adematous forms, exceptional cases with general anasarca, ascites and

polyuria, may be mistaken for beriberi.

The lesson to be learned from this statement is the overwhelming importance of blood examination in all cases of fever in malarial countries or in patients who have lived in those countries, no matter how closely the clinical condition simulates other diseases. The finding of malaria parasites, however, does not rule out the co-existence of other diseases, and acute judgment is needed in the evaluation of signs and symptoms.

Differential diagnosis of blackwater fever.-The diseases with which blackwater fever might be confounded are—(1) paroxysmal hæmoglobinuria; (2) bilious remittent malaria; (3) yellow fever; (4) leptospirosis; (5) favism. If it be borne in mind that rigor, hæmoglobinuria and pyrexia are all in evidence at the outset in blackwater fever, and also that blackwater fever is acquired only in certain countries, an error in diagnosis is improbable.

PROGNOSIS OF MALARIA

As a general rule, malaria is a much more serious disease in children than in adults. It is a serious disease in the weakly, especially in those whose constitutions are undermined by any intercurrent disease, such as phthisis or dysentery. It may lead to abortion in pregnant women, and this possibility must always be considered.

TREATMENT OF MALARIA

(Benign Tertian, Quartan, Ovale Tertian and Subtertian)

General management of a case of malaria.—Every case of malaria with fever should be nursed in bed and treated seriously, for severe symptoms may develop at any moment; he should remain confined to bed till he has been afebrile for 48 hours. The room should be darkened to mitigate the photophobia; a sports shade or eyeshade serves this

purpose very well.

Special attention should be paid to clothing; the patient's feet must be kept warm with bed-socks, and after the stage of perspiration the bedclothes should be changed. Attention to the food is also necessary. During the acute stages it is best to give plenty of water and lemonade to drink, while the food itself should be fluid and easily digestible. During the convalescent stages, if the patient has an appetite, full diet should be substituted, and there is no point in denying to patients who are used to it a strictly moderate amount of alcohol; beer and stout in moderation are useful.

For three hundred years it has been almost universally believed that in quinine medical science possessed a unique and specific remedy for this fever—a remedy unrivalled throughout the whole range of medicine in its potency and effects; but during the last twenty years, synthetic specific remedies—atebrin, paludrine, plasmoquine, chloroquine and daraprim

have been synthesized.

Antimalarial drugs fall into 6 groups-

(1) Cinchona alkaloids, including quinine.

(2) 4-aminoquinolines, including chloroquine, sontochin, camoquine.

(8) 8-aminoquinolines, including pamaquin, pentaquine, isopentaquine and primaquine.

(4) Diguanides, which includes proguanil.

(5) Acridines, which includes menacrine.

(6) Pyrimidines, or daraprim (pyrimethamine).

The Germans followed the idea that methylene blue might produce an effective drug, because it enters the malaria parasite by staining it. They introduced basic side chains of various kinds into the quinoline nucleus and synthesized pamaquin (plasmoquine). Roehl showed its action on blood-forms of P. relictum in canaries, and now it has been proved that it has an action on exo-erythrocytic forms. As this drug proved toxic to humans they put side-chains which they evolved into other heterocyclic nuclei and finally produced mepacrine (atebrin). When the right hand link of atebrin is removed a quinoline compound with a side chain, still opposite the nitrogen, results and this is chloroquine. Next sontochin with an extra CH₂ group was prepared.

Proguanil (paludrine) is a completely new type.

Toxicity.—The toxic effects of these groups of drugs are dealt with under each heading, but it should be remarked that with the 8-aminoquinolines the margin between effective and toxic doses is relatively small. The commoner side-effects are abdominal pain, discomfort and cynosis, but the most dangerous (especially in coloured races) is hæmolytic anæmia.

Of all the antimalarial drugs proguanil (paludrine) has the widest range

between effective doses and those producing side-effects.

I. QUININE

Quinine is an alkaloid isolated from the bark of the cinchona tree, originally a native of South America, but now cultivated in Eastern

countries, especially Java, where the most prolific variety, C. ledgeriana, has been produced. Recently this drug has been successfully synthesized by Woodward and Doering in America. There are many salts of quinne.

though at present most are merely of historic interest.

When taken by the mouth cinchona alkaloids are rapidly and completely absorbed from the intestinal tract, but the plasma concentration falls rapidly after cessation of administration. After oral or intravenous administration this drug is found in considerable amounts in the pancreas, liver, spleen, lung and kidney. Solutions of quinine decrease in antimalarial activity when exposed to ultraviolet light.

Quinine hydrochloride¹ is fairly soluble and is the form most usually dispensed. The sulphate is cheaper, though almost insoluble in water. Sugar-coated pills are effective and are easy to swallow. To dissolve the sulphate 10 minims of acid. sulph. dil., or acid. phosph. dil., should be

added to every 10 gr. of quinine sulphate.

To disguise the bitter taste the addition of syrup of orange or glycerine is useful, or when dissolved in milk; a special preparation is *Lucquin* (Cow and Gate, Ltd.) in powder form, containing quinine ethyl carbonate, 2½ gr. to the teaspoonful, which is suitable for children.

Other forms of quinine.—Euquinine, or the ethyl carbonate, has the advantage of being tasteless as it is practically insoluble and is specially suitable for children. Quinine alkaloid, though almost insoluble, appears to be absorbed from the intestinal tract.

Five different alkaloids are known from the einchona bark, but of these quinidine and cinchonine alone have any action on malaria, especially benign tertian and quartan.

Dosage of quinine.—The maximum dose for the adult European is about 30 gr. (2 grm.) daily. Larger ones than these are toxic and, as frequently proved, not more efficacious.

For children the dose is one-twentieth of that of the adult for each year of age. A child of five should receive one-quarter of the adult dosage, whilst to those above fifteen the adult dosage may be given.

Quinine in pregnancy.—It is a popular belief, that excessive, almost poisonous, amounts are necessary to bring about abortion. Indeed it may be truly said that a pregnant woman runs more risk of miscarriage and detriment to health from repeated attacks of fever than from reasonable quinine therapy. In small prophylactic doses it does not interfere with menstruation, conception or pregnancy, though some think that the focus may be affected. In the puerperal state, which often has the effect of stirring up anew a latent malarial infection, a dose should be taken occasionally.

Excretion of quinine.—It has been shown that quinine is excreted in the same manner by whichever route it is administered. It appears in the urine within 15 minutes and one-quarter of the total is excreted by this route, and the highest concentration is 7-11 gr. quinine base per litre. Large amounts are excreted in the fæces. This holds good only for the tannate or carbonate, not for hydrochloride, hydrobromide, bisulphate, sulphate or even for the insoluble ethyl carbonate.

¹Quinine hydrochloride has a pH of 6.5; the dihydrochloride 3.5. Contrary to what is usually stated the former is suitable for parenteral injection and is indeed less painful than the dihydrochloride.

The Tanret¹ reaction in the urine has given important indications in the treatment of subtertian malaria (Howie and Murray-Lyon, 1943), especially regarding absorption of quinine. The majority give positive reactions between one and five hours after the exhibition of quinine. In some the reaction may remain negative until intravenous quinine has been given. A most practical method of ascertaining whether quinine is being absorbed consists of coating quinine pills with methylene blue, which discolours the urine green.

Quinine, in prophylactic doses, is excreted in the milk of nursing mothers, as can be demonstrated by a modification of the Tanret method. Excretion

commences in fifteen minutes and is completed within one hour.

It has been suggested that quinine therapy is aided by the addition of alkalis, but this is no longer regarded as important.

In naturally acquired malaria, especially benign tertian, continuous and prolonged quinine therapy may be of little benefit in preventing relapses. Therapeutic or malaria induced by blood-inoculation appears to be extraordinarily amenable to quinine treatment.

Cinchona febrifuge (30 gr. daily) contains all the alkaloid of chinchona (C. succirubra) bark and gives much the same effect as quinine (Fletcher concluded that in 20 gr. daily the four alkaloids—quinine, quinidine, cinchonine and cinchonidine—appear to be of equal value in controlling benign tertian malaria, but that quinidine sulphate is of special value in quartan fever).

Java febrifuge contains 11.5 per cent. of quinine and a small percentage (5 per cent.) of quinidine. In India Cinchona febrifuge is issued in 3 gr. tablets and is widely used in that country as a substitute for quinine on account of its cheapness. It is also prescribed in 10-gr. doses together with citric acid and magnesium sulphate.

Quinetum is a preparation consisting of quinine, cinchonidine and cinchonine

in equal parts.

Totaquina is another preparation standardized to contain not less than 70 per cent. of crystalline alkaloids of which 15 per cent. is quinine. Two types are dispensed in India. Type I consists of chiefly quinine and cinchonidine; in Type II the chief alkaloid is cinchonine.

Quinine is best given to patients in the sweating stage and its action is enhanced by simultaneous aspirin and aided by copious drafts of lemonade or water.

Action of quinine on malaria parasites is by no means clear, and it is not known whether it is direct or indirect. It appears to act on the merozoites rather than on the trophozoites, by the fact that it exerts the greatest effect an hour before the malarial rigor. The fact that malaria parasites, on addition of quinine saline solution of 1:10,000 for 12 hours, are still capable of producing infection in volunteers when injected provides strong evidence against the belief in direct action. Probably, as Shute has shown, various strains of malaria parasites exist in the same species and this explains the varied response, especially in benign tertian. The distribution of quinine in the body has been the object of much research and some think that it is stored in the liver, but in monkey-malaria, Nauck and Malamos have shown that the action is not interfered with when the main protective organ (the spleen) is removed. Probably in complete cure both methods of action come into play, but direct action occurs first as seen in the instantaneous results of intravenous injection. Solutions of quinine decrease in antimalarial activity when exposed to ultra-violet light.

¹ The Mayer-Tanrel reaction consists of two solutions:—A, Mercuric chloride 1.35 grm. aq. dest. 75 ml.; B, Potass. iod 5.0 grm. aq. dest. 20 ml. The two solutions are mixed in 100 ml. aq. dest., plus 10 ml. urine to each of two tubes. If they remain clear, quinine is not present, if turbid it is. Albumin is removed by a drop of acetic acid.

Toxic effects of quinine.—The milder manfestations are nausea, tinnitus, dizziness, tremors and palpitations. Vomiting is occasional and may be controlled by 10-20 min. of 1:1,000 adrenalin injected with

& oz. of water.

Idiosyncrasies are exceptional—some become hypersensitive from long-continued dosage. In others it produces urticaria: in others again, cutaneous eruptions varying from a mild erythema to weeping eczema, or an exfoliative dermatitis. An indication of sensitivity may be obtained by the "scratch test" (endermic reaction). A drop of 1:10 solution is applied to a scratch on the forearm and, when positive, a zone of crythema and cedema results. Saline controls should be employed. Local cedema of the eyelids as well as irritation of the nasal and oral mucosac have been recorded. Cutaneous hæmorrhages, approximating to purpura, with bleeding from the mouth, bladder and rectum are rare; occasionally quinine hæmoglobinuria resembling blackwater fever has been recorded. In heroic doses mental confusion and even coma may ensue.

Contrary to popular belief there is no evidence that permanent deafness

may be brought about by quinine.

Quinine amaurosis, or amblyopia, generally results from gross overdosage (80-160 gr.), but exceptionally in those with pronounced idiosyncrasy, temporary blindness may follow even moderate doses. According to McGregor (1944) this is due to damage to the retinal cells with the production of a "sieve-like" field. The milky appearance is attributed to ischæmia and the cherry-red spot in the macula to blockage of the central artery. Total blindness may ensue when the arteries become narrowed, which may be due either to arterial spasm or to thickening of the intima. The primary lesion is said to be in the ganglion cells of the retina. This ambly opia recovers spontaneously, but improvement may be very slow. Strychnine is given in large doses and vasodilators, such as amyl nitrite.

Injections of Quinine

(a) Intramuscular injection

This method has been much criticized. The general consensus of opinion is that it is a valuable therapeutic measure under certain circumstances. Its dangers have been much exaggerated and probably are due to abuse.

The indications are non-absorption of oral quinine owing to severe vomiting, the presence of several toxic symptoms or of large numbers of parasites in the peripheral blood. The most suitable salts for this purpose are the hydrochloride, or the dihydrochloride which is soluble in its own weight of water. Pain is caused by the acidity of the solution; that of the latter is pH 3-5, of the former 6-1. For that reason the hydrochloride salt is to be preferred. The hydrochloride is best when combined with urethane.

Solvechin, on account of the correction of the pH to that of the tissue, is recommended as the ideal preparation for injection (25 per cent. solution

at pH 7.2); 2 ml. contain 0.5 grm. quinine dihydrochloride dissolved in phenyl dimethyl pyrazolon, which acts as an analgesic. In chronic benign tertian malaria 2.2 ml. are injected twice daily, if necessary for four days or longer. In subtertian malaria it is effective in the acute stages. Quinine lactate has also been recommended as being less irritating.

Site.—The usual site for injection is the gluteus maximus muscle at a point on a horizontal line through the apex of the great trochanter (Fig. 8). This point lies well above the exit of the deep-lying great sciatic nerve, which may be injured by plunging the needle below the fold of the buttock so that paralysis of the leg may result. Pain is minimized and absorption aided by massaging the site of injection for some three minutes. A stout, preferably platinum-iridium, needle is driven home rapidly deep into the muscle after cleansing the skin thoroughly. Should the salts of

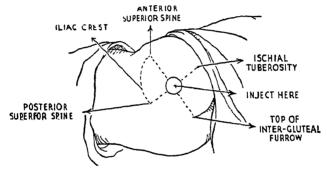


Fig. 8.—Diagram showing the site for a quinine injection.
(Burroughs, Wellcome & Co.)

quinine be used in tabloid state, their solution must be freshly prepared and boiled and the syringe and needle thoroughly sterilized. In children, especially, the injection should be given slowly and in dilute solution. It has been shown that concentrated solutions of quinine are rapidly absorbed from the tissues and that its action upon the parasites in the blood is rapid.

Localized necrosis of the muscular fibres is apt to occur after quinine injection. This is followed by ædema, possibly by destruction of the blood vessels, thus creating a favourable culture ground for tetanus and other organisms (Fig. 9). Thus, in addition to tetanus and abscess formation, gas gangrene and streptococcal septicæmia may ensue. No advantage is gained by repeating the injection in approximately the same area. This procedure is dangerous by promoting extensive hæmorrhage and necrosis.

Three or four intramuscular injections suffice to tide over the pernicious symptoms of subtertian malaria, whilst continued pyrexia may not always indicate persistence of malaria parasites, but may be due to toxic absorption from injections.

Quinine injections, when excessive, may occasionally give rise to fibrous nodules about the size of almonds which may persist for years and give rise to much pain. They may even break down and suppurate.



Fig. 9.—Quinine abscess of buttock developing ten weeks after last quinine injection.

(b) Intravenous quinine injections.—In the pernicious or acute forms of subtertian malaria, especially when there is cerebral involvement, where it is important to obtain rapid and powerful action, quinine should be injected intravenously. The hydrochloride or dihydrochloride salt should be employed in doses of 10 gr. dissolved in 10 ml. of distilled water. In algid cases or those with cardio-vascular collapse it is advisable to reinforce with glucose, 5 per cent. in saline in amounts of ½ to 1 pint. The solution of quinine should be boiled in a test tube, drawn up into a sterile syringe and injected into the median basilic vein. On introduction the plunger of the syringe should be withdrawn slightly to permit blood to enter the barrel. The injection should be made slowly and at least three minutes spent over the operation. One dose of 10 gr. usually suffices to stop the fever and to cause disappearance of most of the parasites within eighteen hours.

It is sometimes advantageous to follow it up with an intravenous injection of 10 min. of adrenalin (1:1,000). When the myocardium is involved especial care is necessary, since the toxin liberated by rapid destruction of parasites may paralyse the cardiac mechanism. It is then more advisable to commence with a preliminary intramuscular and to follow this up, some six or eight hours later, with a smaller intravenous injection (6 gr.). There is usually a considerable fall in blood-pressure. When there has been great destruction of erythrocytes a blood transfusion

of 300-500 ml. is indicated. Continuous intravenous drip method of quinine injection is recommended by Strahan (1948) in heavy P. falciparum infections. The solution should contain 0.06 grm. (1 gr.) quinine bihydrochloride, or hydrochloride, to 2 ml. of sterile saline. The rate of injection is 2 ml. per minute and the total amounts given are 0.5 grm. (7½ gr.). In one case a total of 2 grm. was given in two hours.

The Ascoli treatment was introduced in Italy for the treatment of malarial cachexia resulting from chronic subtertian infections. The method consists of intravenous adrenalin injections of $\frac{1}{100}$, $\frac{1}{20}$, $\frac{1}{80}$ mgm. in gradually

increasing doses up to 1 mgm., combined with quinine treatment.

II. 4-AMINOQUINOLINES

Chloroquine (S.N. 7618) (for synonyms, see p. 871) was originally synthesized by Andersag, Breitner and Jung (1937), but is now produced in the United States. The drug concentrates in the liver and is an active schizonticide in P. vivax malaria. The salt usually employed is the diphosphate. Tablets of 0.25 grm. contain 0.155 grm. of the base. maximum initial dose (Handfield-Jones) is 1.0 grm., followed after 6 hours by 0.5 grm., then 0.5 grm. on second and third days. The duration of the fever is cut short with this drug, usually lasting about 80 hours. Others have reported equally good effects with smaller doses, such as 0.5 grm. followed by 0.25 grm. after 6-8 hours, and then a single dose of 0.25 grm. on each of three successive days. It is a powerful schizonticide which appears to have an action similar to that of quinine and exerts a suppressive effect when given once weekly in doses of 0.5 grm. By intramuscular injection chloroquine can be given a dose of 200 mgm. of the base¹ repeated in four hours, but oral treatment should be started as soon as is possible. In the form of the dihydrochloride it has been injected intravenously in doses of 5.7-14.9 mgm. of base per kg. body weight. A reasonable dose is 5 ml. of a 5 per cent. solution.

Side-effects.—In very large doses chloroquine may produce difficulties in vision, bleaching of the hair, slight weight loss and headaches. Occasionally vomiting and gastric disturbances have been reported.

Sontochin, or sontoquin (S.N. 6911) appears to have a very similar action. Comoquine ("Cam-aqi") (see p. 871) is given as the bihydrochloride in tablets of 0.2 grm. by mouth. The single dose is 0.6-1 grm. for adults and for children it is given on the basis of 10 mgm. per kg. body weight. Thus those of five to fifteen receive 0.2 grm. and over that age 0.4 grm. As a suppressive it is said to be more effective than chloroquine in doses of 0.6 grm. weekly.

Nivaquine B (May and Baker) is chloroquine sulphate in tablets of 0.2 grm., containing 15 mgm. of the base. It has the same therapeutic

action as the diphosphate.

III. 8-AMINOQUINOLINES

Pamaquine (plasmoquine—for other synonyms see p. 877). On account of its toxicity the doses are small. In doses of 0.04 grm. daily it acts as a schizonticide in P. vivax and P. malariae malaria, but is less effective in P. falciparum. It is a powerful gametocide in all malaria infections.

10-6 grm. of base equals 1 grm. chloroquine diphosphate.

Gametocytes are destroyed before the schizonts and crescents of P. falciparum disappear after five days' dosage. The changes are characteristic. resulting in disruption of chromatin and dispersal of pigment. In combination with quinine it was formerly much used in treatment of P. rivax malaria in which it is a suppressant. Such a combination in tablet form was known as pamaquine (or plasmoquine) compound each containing 0.01 grm. pamaquine with 0.125 grm. quinine sulphate. Quinoplasmine (Chinoplasmin) is 0-1 pamaquine and 0-3 grm. (41 gr.) quinine. The dose was three tablets daily for adults. In this dosage it was employed by Manifold in India in 1930 for suppression of P. vivax malaria in British troops (three weeks' course of pamaquine 0.02 grm. with 10 gr. (0.75 grm.) quinine, every morning and evening). The addition of quinino is considered to counteract the toxic effects of pamaguine. These may be severe. The commonest is cyanosis (drug methamoglobinumia), abdominal pains, vomiting; and most severe of all, methamoglobinuria (especially in P. falciparum). This is due to intravascular hamolysis and resembles blackwater fever also in the pathological effects. Toxic hepatic necrosis and hamorrhagic nephritis may also ensue, and there is some evidence that it may provoke blackwater fever. Parenteral injections are dangerous.

The combination of pamaquine and atebrin is not generally recommended. This is known as "Atepe" (atebrin 0.1 grm. and pamaquine

0.005 grm.).

Pentaquine (S.N. 13,276) is said to be half as toxic as pamaquine, but twice as active, and isopentaquine even less toxic and equally effective.

Pentaquine in the form of yellow needles is slowly soluble. In prolonged treatment of 60 mgm. with 20 gr. quinine it enhances the action of the latter and eradicates P. vivax. It is said to be toxic for negroes and children. (For treatment of benign tertian malaria, see p. 93, Coggeshall and Rice, 1949.) A compound of quinine sulphate with pentaquine phosphate has now been prepared under the name of Quiniplex for the treatment of P. vivax malaria. Each tablet contains quinine sulphate,

150 mgm. with pentaguine phosphate 6.5 mgm.

Primaquine (S.N. 13,272) (see p. 878) in the form of diphosphate, is a compound closely allied to pamaquine and has been used together with quinine in reducing the relapse rate of the Chesson strain of *P. vivax* malaria (Edgcomb and colleagues, 1950). On an equal weight basis it is claimed that primaquine is four times as active as other members of this group. It has a high prophylactic as well as curative ratio when administered in safe therapeutic daily doses. In these respects primaquine is superior to both pamaquine and isopentaquine. A daily dose of primaquine is given concurrently with 1.0 grm. of quinine sulphate. Larger doses are not recommended.

IV. DIGUANIDES (PROGUANIL OR PALUDRINE)

Proguanil (Paludrine M. 4888, see p. 877) was discovered by Curd, Rose and Davey in 1945. This drug represents a complete departure from any other antimalarial drug. It is N-p-chlorophenyl-N5—Isopropylbiguanide acetate. The salts most used are the monoacetate and the monohydro-

chloride. In fowl malaria (*P. gallinaceum*) it has a powerful action on the erythrocytic forms as well as on the pre-erythrocytic (EE forms) in the tissues. In human malaria the action appears to be similar. Its chief advantage is that it is an active prophylactic and suppressant of malaria.

It is moreover easily tolerated and toxic side-effects are few—such as nausea, vomiting and gastric discomforts. In very large doses, such as

1 grm., it may very rarely precipitate hæmaturia.

As a therapeutic agent it possesses many advantages and does not, like atebrin, discolour the skin, nor does it produce the unpleasant tinnitus of quinine. Paludrine apparently reduces the secretion of gastric juice which may be related to the gastro-intestinal symptoms which have sometimes been recorded (Doll and Schneider). It is rapidly absorbed and excreted in the urine and, though blood concentration is much diminished twelve hours after administration, a satisfactory build-up can be effected if doses are taken twice daily.

When paludrine is given in 100-800-mgm. daily doses to *P. falciparum* or *P. vivax* gametocyte carriers no effect is observed on the number or microscopic appearances of the gametocytes in the blood, but when given early in the attack, gametocyte production is affected indirectly by checking the primary trophozoite wave before gametogony has occurred. Though gametocytes of both *P. vivax* and *P. falciparum*, when ingested by mosquitoes, undergo exflagellation and fertilization, and may even produce small oöcysts, further development ceases, and it has been shown that complete sterilization of the gut infection of mosquitoes results within 1-2 hours after 150 mgm. of paludrine has been administered to a carrier.

Paludrine acetate, or preferably the lactate, has been used for intravenous injection in doses of 25 to 400 mgm. and in some instances it has to be repeated. In comatose cases it is not nearly so efficacious as

intravenous quinine (Chaudhuri).

For subtertian malaria the optimum dosage appears to be 100 mgm. three times daily for 7-10 days. In view of the rapidly acquired paludrine-resistance, Maegraith and others now advocate 600 mgm. daily. For benign tertian and quartan larger doses are indicated, such as 250 mgm. three times daily for the same period, though this treatment does not appear to extirpate *P. vivax* from the circulation any more effectively than does quinine, though a single dose of 100 mgm. is enough to suppress an individual attack.

Fairley and his co-workers have asserted that combined paludrine (800 mgm.) plus 80 mgm. plasmoquine base daily for 10 days did not retard relapses, though superior to quinine-plasmoquine suppressive treatment (interval between treatment and relapse was 66.5 days with the former and 81.4 days with the latter). It was concluded that this was due to the inhibiting action exerted by paludrine on the late pre-erythrocytic forms of $P.\ vivax$.

Williamson, Bertram, Lourie, Bishop and Birkett (1947) have shown that *P. gallinaceum* in chicks becomes readily paludrine-resistant and that this may also take place in *P. vivax* and in *P. falciparum* in man.

Covell, Nicol and associates (1949) have now concluded that paludrine has a less rapid action than has mepacrine or quinine, so that, in order to

prevent relapses in *P. falciparum* malaria, reinforcement with mepacrine or quinine is necessary. Adams has shown that paludrine resistant strains subsequently rapidly yield to atebrin treatment.

Carrington, Crowther and others (1952) have shown that in the body of experimental animals and man proguanil is metabolized into a derivative

which is 10 times more active against P. falciparum.

Proguanil resistance.—Proguanil-resistant strains of P. gallinaccum have been prepared by Bishop and Birkett and it was found that this character was retained for some months. They also showed that a similar resistance could be produced for sulphadiazine. Similar resistance is found in P. cyromolgi in monkeys. In P. vivax of the Chesson strain resistance of more than one thousand-fold has been produced by Cooper, Coatney and Imboden (1950). It is suggestive that the antimalarial action of sulphadiazine and sulphanilamide is inhibited by P.A.B.A. (p-amino-benzoic acid). The gradual development of resistance in Malaya and Indonesia has been described by Edeson and Field. When first introduced the response to naturally acquired P. falciparum infection was good. During 1947 little was found to choose between a single proguanil dose of 100-300 mgm, and a course of 300 mgm, daily for two days. The fever and parasitæmia cleared at the same rate. Since 1948 resistant cases have been frequently encountered and one case out of every four was found to be so. In rubber estates where this condition was found the labourers had been subjected to proguanil suppression for more than two years. When used in mass treatment this resistance is so rapidly acquired that it is transmitted through the mosquito (Seaton and Adams).

V. ACRIDINES (ATEBRIN OR MEPACRINE)

Atebrin.—(For synonyms, see p. 875). This is the dihydrochloride of 2-methoxy-6-chloro-9 (4'-diethylamino-1'-methylbutyl) aminoacridine, a bitter yellow acridine dye, usually prepared as the hydrochloride. A more soluble salt for injection is known as "musonate." The former dissolves in water at 40° C. in 7 per cent. solution.

Kikuth originally proved that atebrin exerts a specific schizonticidal action on all malaria parasites, but has not direct action on gametocytes (especially P. falciparum). It attacks early trophozoites first, then developmental forms, though if given over a sufficiently long period, gametocytes disappear. Exflagellation is not interfered with.

The most beneficial effects of atebrin are seen in the treatment of subtertian malaria and there appears to be little doubt that by its extended use during the recent world war the incidence of blackwater fever has been thereby greatly reduced, though occasionally it may ensue after intensive atebrin treatment. The results in benign tertian and quartan infections have been less satisfactory.

Atebrin accumulates in the body and stains the tissues and skin yellow. It is specially stored in the liver, spleen and reticulo-endothelium. Elimination is slow and may take a month to complete. The yellow discolouration of the skin may be mistaken for jaundice. The sclerotics are rarely affected, though little correlation has been found between the plasma concentration and therapeutic effect. It has to be distinguished from infective hepatitis, acholuric jaundice, pernicious anæmia and carotinæmia.

Long-continued administration may be associated with an increased

incidence of lichen planus (Nisbet and Schmitt, 1945). Other skin lesions have been described, including lichenoid dermatitis, eczematoid and exfoliative dermatitis. The lichenoid lesions are localized erythematous plaques on dorsal surfaces of hands and feet; subsequently similar lesions have been noted on the mucous membranes. Urticaria has also been recorded. Ginsberg (1946), confirmed by Kierland, has demonstrated the interesting phenomenon that, in persons taking suppressive atebrin, the finger and toe nails emit a greenish-yellow phosphorescence when exposed to Wood's light (an ultra-violet ray filtered through glass containing nickel oxide). This restricts the passage of all but relatively long wave ultra-violet light (about 3,650 A). Periorbital eczema with corneal cedema has been reported and after prolonged administration a peculiar brown discoloration of the nails may ensue.

Another serious idiosyncrasy is cerebral excitation, especially when atebrin is given in large doses. Some serious cases resemble schizophrenia, especially in some sensitive Europeans, but more commonly in Malays,

Tamils, Chinese and Sinhalese (Green, Hoops, Kingsbury).

American observers (Gaskill and Fitz-Hugh, 1945) found out of 7,604 cases of malaria treated with atebrin 0.4 per cent. developed a toxic psychosis. The total amount was 2.1 grm. The time of onset varied; the most rapid was on the third day (0.9 grm.). The latest date was six days after the completion of treatment. The onset was often insidious and declared itself in a sudden increase of motor and psycho-motor activity with auditory and visual hallucinations, delusions and sometimes disorientation. The effect was usually euphoria and expansiveness. The average duration was 23 days, but the great majority who recovered from the initial psychosis were re-treated with atebrin without any further manifestations.

Atebrin is well borne by pregnant women. Its most valuable property, in addition to its prophylactic properties (p. 103), is, like quinine, its high power of preventing relapses in subtertian malaria. Its action on relapses

of benign tertian and quartan is less satisfactory.

Atebrin is probably equal in therapeutic value to quinine, but its action is slower, especially in acute subtertian malaria, but it gradually influences the fever and destroys the parasites. Children tolerate atebrin well. Atebrin is dispensed in tablets of 0·1 grm. (1½ gr.) and is usually given three times a day on a full stomach. In order to obtain solution it is recommended that a glass of water should be drunk simultaneously. The daily dose is 0·3 grm. (4½ gr.) for 7–10 days. It is customary to give a "loading dose" of 0·6 grm. or even 0·9 grm. for the first two days of treatment, but plenty of fluid (hot tea) must be given at the same time. For small children the daily dosage of 0·03 grm. is best given in milk or concealed in raisins. Atebrin treatment can be combined with 5–10 gr. of quinine hydrochloride daily.

For children the following doses are recommended:

Intramuscular injections are less painful than those of quinine. Two injections with an interval of 24 hours are recommended. The soluble form (atebrin musonate) is supplied in ampoules containing 0-1 or 0-3 grm. and the contents are dissolved in 3 or 9 ml. of water respectively. In severe subtertian infections its action is not so rapid as is quinine. With the strength of atebrin (0-3 grm. in 9 ml.) the dose is:

6 months to 2 years . . . 1 ml. 2-4 years 2 ml. gradually increasing to 7 ml. at 15-18 years.

Intravenous injections of 0.2 grm. of atebrin musonate have been given in cerebral malaria, but are not as efficacious as quinine. This amount should be diluted with 9 ml. of water.

An interesting outcome of atebrin treatment in its application to lupus erythematosus by Page (1951). Eighteen cases were treated and one failed to improve. In a few, all lesions completely disappeared within six weeks of commencing treatment and in two associated rheumatoid arthritis also improved.

Atebrin tablets deteriorate in damp heat. This is prevented by packing in flexible waterproof sheeting (polythene, I.C.I.). This substance retains its flexibility in extremes of heat and cold.

VI. NEW COMPOUNDS AND OTHERS

Daraprim (pyrimethamine).—B.W. 50-63 (Archibald, 1951) belongs to a class of compounds hitherto unused against malaria (see p. 872). When tested out against P. gallinaceum, P. cynomolgi and P. berghei it is 68 times as active as proguanil, but has no pronounced action on the pre-crythrocytic stages. In doses of 5 mgm. in African children it is as effective as larger ones against trophozoites of P. falciparum and P. malaria. Daraprim is clearly a powerful schizonticide. A single dose of 0.5 mg. per kg. causes the disappearance of asexual forms of these parasites from the blood. The rate with which it eliminates parasitemia is quicker than that of proguanil. Its small effective dosage and tasteless character make it the drug of choice in the treatment of malaria in infants and children (McGregor and Dean Smith, 1952), and in doses of 5 mgm. daily it has been shown to be an effective malaria suppressant (Goodwin, 1952).

In Malaya, Field, Wilson and Edeson found it failed to cradicate ascaula P. falciparum parasites. A total dose of 300 mgm. failed to cure 7 out of 26, though East African strains are much easier to cure with this drug. There were no failures in patients with P. vivax for which this drug appears most suitable. In Assam and N. Bengal, Gilroy, Norman and Arthur found few failures with single doses of 20 or 50 mgm. and great rapidity of action was observed with P. vivax. Schneider, Canet and Dupoux used it for patients infected with P. falciparum and P. vivax in Tunisia and Indo-China. They found a single dose of 50 or 100 mgm., or two doses of 50 mgm. effective. Foy and Kondi (1952) have recently shown that P. falciparum gametocytes from a patient treated with daraprim failed to develop to the sporozoite stage in mosquitoes fed upon his blood. Toxic side-effects of daraprim appear to be negligible.

Paludrine-resistant parasites are amenable to daraprim as so well shown by Avery Jones in a self-inflicted experiment in Nairobi with a strain of *P. falci*-

parum imported from Malaya (1953).

Azacrin (an acridine, see p. 820).—A new compound (Ward and Blenkinsop) tested in W. Africa by Bruce-Chwatt and Archibald (1953) in tablets of 0.2 grm. Children are given 2 tablets, followed by 1 on each of the two following days. Adults tolerate 2 tablets daily, but more may provoke vomiting. The clearance time for P. falciparum was shortest (1.58 days) with this drug.

Sulphonamides.—Sulphanilamide and sulphanyl-sulphanilate have been proved specific in ape malaria (*P. knowlesi*) by intraperitoneal injection. Later it was found that sulphathiazole in doses of 6 grm. daily for five days extirpates *P. vivax* (Pakenham-Walsh and Rennie). Sulphadiazine has been found by Fairley to have the same action.

Salvarsan and its derivatives appear to exert some action on *P. vivax* but little or none on other species. *Stovarsol*, in 4-gr. tablets, twice daily for 10 days, has been credited with some curative effect in stubborn benign tertian infections.

Mapharsen (meta-amino-parahydroxy-phenylarsine oxide) intravenously is said to cut short a malarial attack in doses of 0.04-0.06 grm. according to body-weight, and is said to be of special value in controlling therapeutic malaria.

Thiobismol (sodium-bismuth thioglycollate), injected intramuscularly in 0.2-grm. doses, exerts a peculiar action upon therapeutic benign tertian malaria and produces remissions of 48 hours and is therefore of value in this form of treatment in cases with cardiac embarrassment. After such an injection quinine and atebrin appear to act quicker.

TREATMENT OF BENIGN TERTIAN, QUARTAN AND SUBTERTIAN FEVERS

During a paroxysm of benign tertian it is better to give quinine or paludrine during the rigor or hot stages and not to wait, as formerly advocated, till the patient commences to sweat; but in subtertian malaria, especially, it is wise to commence treatment directly diagnosis is established. Ten grains of quinine (0·1 grm. paludrine or 0·25 grm. chloroquine) should be administered and thereafter in 10-gr. (0·65 grm.) doses three times daily after meals for the next three days (or paludrine 0·1 grm. three times daily). Should the patient be constipated a saline purge should be given, but if he presents severe toxic manifestations, as in subtertian malaria, one should not hesitate to inject quinine intramuscularly or, when signs of cerebral irritation are present, intravenously. The sooner a case of subtertian is energetically treated the less chance there is of relapse or development of pernicious symptoms. It is a wise plan for the patient to take, once a week, a mild saline. For the anæmia, iron and arsenic in pill or tabloid form are of value.

Hæmatinic plastules (liver and iron, Wyeth), 4-6 daily, are to be recommended. In the severe anæmia of subtertian malaria intramuscular injections of liver (plexan, hepatol, or campolon), 4 ml. twice weekly, will restore hæmopoiesis. Sometimes, however, blood or plasma transfusions may be necessary. Rest is an important factor and it is true that the malignancy of subtertian is much greater under war conditions than

in civil life. For the headache and supraorbital neuralgias which so often follow malaria nicotinic acid is recommended.

In the confusion that is bound to ensue at the present time in the presence of so many new synthetic antimalarial drugs it is difficult to be precise and dogmatic. Chloroquine diphosphate now enjoys a reputation in the treatment of all forms of malaria in the doses advocated (see p. 871). For anti-relapse treatment of benign tertian (P. vivax), which has always been unsatisfactory, the best results which have now been obtained are by a combination of pentaquine, 60 mgm. daily with 20-30 gr. of quinine for 14 days. This has resulted in the termination of relapsing war-contracted vivax malaria in 163 out of 185. Toxic reactions are minimal (Alving, 1948, Coggeshall and Rice, 1949). By this method eradication of relapsing P. rivax malaria was achieved in 98 per cent., but using only 30 mgm. pentaquine daily (Strauss and Gennis, 1950). Primaquine (see p. 878) is now being tested out on American troops with favourable results. Hulshoff (1951) has found also nivaquine C (French resochin preparation almost identical with chlorogume). 100 mgm. for 5-7 days followed by pamaquine naphthoate 18 mgm. thrice daily for 5-6 days reduced the relapse rate from 58 per cent. to 30 per cent.

Treatment of bilious remittent subtertian malaria, or cases of malaria with intense icterus, should be conducted on the same general lines as for blackwater fever. All solid food should be withheld and sips of glucose solution substituted. Directly the diagnosis is established full doses of paludrine should be given, or if the action of this drug is not sufficiently rapid, an intramuscular quinine injection. The vomiting may be controlled to some extent by the administration of sodi. bicarb. solution, 1 drm. to the pint, whilst, if the patient is very restless, an injection of phenobarbitone (gr. 5) is indicated. This is specially valuable when there is violent delirium.

Treatment of cerebral malaria.—The onset of cerebral malaria is to be suspected when the patient becomes drowsy or disorientated. Good nursing is most important. Ice-bags should be applied to the head and hot applications to feet and legs. The patient should be nursed in a semi-recumbent position and in severe coma artificial feeding may become necessary. If the systolic blood pressure is 100 mm. or over and pulse volume is good, no time should be lost in injecting quinine dihydrochloride intravenously. This should be performed slowly—at the rate of one minute per grain. This can be repeated after an interval of six hours, till the patient is out of coma, but if the systolic blood-pressure is under 100 mgm. and pulse volume is poor, intravenous salines should be given, rapidly at first. Subsequent transfusion of 400 ml. of plasma or glucosesaline by the continuous drip method—40-60 drops per minute—serves to neutralize the toxemia. In order to bring the quinine into intimate dentact with the parasites in the cerebral capillaries, adrenalin, 0.5 ml. of • 1: 1,000 solution, is injected intramuscularly, sometimes intravenously. Should the come not clear up within two hours, intravenous quinine must be continued in doses of 6 gr. at six-hour intervals, but not exceeding a total dose of 80 gr. within 24 hours. Intravenous paludrine has not given such good results (Black).

When convulsions are severe oral administration of nembutal or sodium amytal is useful, but, if there is vomiting, resort must be had to injections. In comatose cases which do not clear up, lumbar puncture and withdrawal of 20 ml. of cerebro-spinal fluid may give relief and this should be repeated daily till clinical improvement is noted. Rogan (1944) advised lumbar puncture in every case as cerebro-spinal meningitis may coexist.

It has been pointed out by Marriott (1945) that life is often threatened by asphyxia and dehydration. The former takes place by the falling back of the tongue, gravitation of the saliva into the trachea, and consequent pulmonary cedema. The maintenance of an airway should be the subject of unremitting care. Dehydration quickly arises from reduction of fluid intake by drowsy, disorientated patients who are also sweating

profusely.

Ransome, indeed, on these considerations, has made it a routine to nurse his patients in the Fowler position. Beneficial effects are due to gravitational decongestion of the brain, whilst the use of the intranasal. intragastric Ryles' tube for continuous drip hydration and nutrition is a life-saving measure. Central cardiac failure may be treated with strophanthin $\frac{1}{60}$ gr. intravenously and repeated after 18 hours, if necessary. Peripheral failure and oliguria should be treated with caffeine sodium benzoate 7½ gr. every six hours.

Scott (1951) has given his experience with chloroquine and intravenous saline. Chloroquine dihydrochloride was used in 10-ml. ampoules each containing 400 mgm. of base. The contents of one ampoule is diluted with 40 ml. sterile physiological saline. The mixture is aspirated with a 50-ml. syringe. Intravenous injection was made slowly (15 min.), controlled by blood-pressure readings. The smallest dose was 5.8 mgm. chloroquine per kg.; the largest 12.5 mgm. Some were treated by intravenous injection of one ampoule in 500 ml. normal saline by intravenous drip and the therapeutic effect was equally satisfactory.

It should be remembered that increasing coma, especially when accompanied by signs of cerebral irritation, is often due to punctate

subcortical hamorrhages.

Treatment of hyperpyrexia.—Hyperpyrexia must be promptly met by prolonged immersion in a cold bath. A good rule is to give it, or cold pack, if the axillary temperature reaches 106° F., but to remove the patient when the rectal temperature registers 102° F. At the same time quinine should be injected intravenously or intramuscularly. If the temperature can be kept down for three or four hours the quinine gets time to act upon the subtertian parasites crowding the capillaries. Antipyretics, such as antipyrin, are worse than useless.

PROPHYLAXIS OF MALARIA

Anti-mosquito measures.—It is obviously impossible to wage war on all mosquitoes. Modern anti-malaria measures are based on the belief that it is more economic and effective to concentrate on the main malariacarriers in each particular district—a procedure known as species sanitation. Some varieties enter dwellings and show preference for human blood and are said to be authropophilic, but the majority are zoophilic and prefer to feed on domestic animals (see Appendix, p. 1026).

The precipitin test is employed for the precise determination of the blood, human or mammalian upon which captured anophelines have fed. The stomach blood is squeezed out on to filter paper, and rubbed well in. The paper should be divided into eight sectors, and blood drops disposed at the periphery. Such specimens can be stored for as long as 3-4 months in a dry place. Then sensitized sera, suitably diluted, are placed into tubes containing 3 ml. of saline and the filter-papers containing the dried blood added. A positive reaction is shown by the development of an opalescent ring at the point of contact; it may appear at once or after incubating at 37° C. Tubes should be inspected at ten-minute intervals up to one hour. Control tests should be performed.

Other factors in planning antimalarial measures govern the principles. The distance between breeding places and dwellings is known as distance of dispersal. In the Oriental region a zone of half-a-mile radius free from breeding-places is found enough to protect a dwelling, but in the Ethiopian region this must be more extensive. Formerly it was thought that, generally speaking, about a thousand yards or one mile between a ship and a malarious shore would secure protection for the crew, but this does not always suffice, because Kligler has shown that, aided by prevailing winds, and especially during hibernation flights, the mosquitoes may travel five miles.

Killing off adult mosquitoes.-Light airy houses with plenty of ventilation, and with no dark corners, discourage the entry of mosquitoes; in the tropics most of the adult insects gain entrance and suck blood during the night. Swatting the resting insects perched on ceilings or walls of dwelling-rooms has been found very effective against A. atroparvus, especially in Holland. Spraying the walls with an insecticide (Pyrethrum-Flit) once or twice a week has been found useful in India against A. culicifacies, especially during the autumn months and in cool weather. The "Freon bomb," a small round drum, containing pyrethrum and DDT concentrate dissolved in dichlorifluormethane, has been evolved by American Army hygienists especially for bodrooms. On opening the nozzle the insecticide is blown out and forms a fine fog, or erosol, which is projected 6-8 feet, killing all mosquitoes in 100,000 cubic feet. Residual DDT spraying kills off anopheline mosquitoes (A. darlingi and K. aquasalis) which are anthropophilic as well as domestic (Giglioli) (see p. 862). The extensive subject of insecticides is treated in Chapter 52 where the different methods of applying DDT and gammexane are described. A note of warning must be sounded against hyper-optimistic expectations of this method. D. B. Wilson thinks that it is unlikely that residual DDT alone will be effective in hyperendemic zones, but where anopheles exist in smaller numbers, as in epidemic or endemic zones, this form of control is successful if applied to large groups of houses. Individual houses will not be protected by residual spraying unless the dosage is about 200 mgm. per sq. ft. or screening is employed as well. In regard to the use of DDT as a larvicide, improvements continue to be made, but the methods have not yet been standardized. of larvicide by aircraft is useful in restricted areas. In rural communities

the simple, yet fundamental, measures like siting of villages and control of water sources still remain of great importance.

Principles of species sanitation.—In this procedure measures are taken to prevent the breeding of dangerous species of mosquitoes; they must therefore be based upon an intimate study of the habits of each. These measures may entail drainage of swamps, if they can be incriminated, but they seldom can. In some cases it is more important to fill in holes and borrow-pits, to camber roads to prevent puddles, and to train the bends of streams or flush them periodically. Marshes, open to the sea, can be periodically flooded with salt water which kills off the larvæ.

In some species of the Anopheles funestus group, and especially for A. minimus, shading of streams prevents breeding, but in this case the amount of overhead cover must be thick enough to prevent the growth of grass. To produce the right degree of shade, lantana (L. aculeata), basak (Adhatoda vasica), and duranta (D. plumieri) have been found suitable in northern districts of India: mugwort (Artemisia vulgaris) for tea, coffee, cardamom and rubber estates in the south.

To prevent mosquito breeding in streams and waterways, it is necessary to get as even and swift a flow as possible without eddies or backwaters. The stream should be canalized, that is to say, the sides should be sloped at an angle of 45 degrees. Embankments should be lined with large stones and the vegetation cleared from the edges. During the monsoon it is especially important to prevent the formation of pools after the subsidence of extra high flood. A stream thus treated is practically self-sterilizing, except with a species of anopheline, such as A. maculatus, which is specially adapted for life in rocky waters. If necessary, canalization should be supplemented by oiling. Subsoil drainage can be employed in place of canalization and, indeed; forms an important feature of estate sanitation in Malaya. Flushing streams with automatic siphons is a modern method.

Seepage, or infiltration of water through bunds or dykes at the bottom of a hill foot, usually forms a fruitful breeding-ground for anophelines. Running swamps in the course of a stream in level country may form dangerous breeding-spots. They can be dealt with by oiling or Paris green. Borrow-pits, formed usually in the process of railway construction, may, when severally earsold, form suitable breeding-places. Tanks, in India and Ceylon, are seldom dangerous, but, if the margins are much overgrown with vegetation, certain anophelines may obtain a foothold.

Rice fields are dangerous when the water is kept in continuous motion through the fields; uncultivated plots in terraced fields that are allowed to become flooded are especially so. In Java the drying-off of the fields throughout a tract on one day each week has been made obligatory and is efficacious without apparently damaging the growth of the rice. To the inexperienced eye there might seem enormous potentialities for breeding anophelines in paddy fields, but the fields themselves are not always so much to blame as irrigation ditches.

Mangrove swamps, especially in the Andaman Islands and West Africa, are associated with virulent malaria due to the breeding of certain species of anophelines, especially A. ludlowi (sundaicus), and A. melas, in saline water. Sunlight also is necessary for the development of these larvæ. Thus, the dense virgin mangrove forest is healthy so long as it is daily traversed by tides; but when trees are cut down, or when bunds are constructed to interfere with tidal movements, and derelict pools are formed which are gradually diluted by rainfall to a suitable salinity, the breeding of anophelines takes place.

Drainage is difficult at sea-level unless there is a big tidal range. In Malaya, owing to the sixteen-foot drop in the tides, it has become possible to install automatic sluice-gates to the bunds.

Smaller collections of water, if overlooked, may constitute a grave danger. A sagging gutter may hold enough water to support large numbers of larvæ; moreover, a good deal of atmospheric moisture is condensed upon the roofs of tropical bungalows so that the gutters are constantly being replenished, even in the absence of rain. Holes in rotten trees may breed a limited number of anophelines; indeed one European species, A. plumbeus, breeds exclusively in this situation. In tropical Africa, A. gambiæ, the most active vector in the world, breeds in collections of water, small or large, of the greatest diversity. The most trivial road puddles, hoof marks or scepages may contain larvæ, as well as the larger collections. Wells are a certain source of trouble where they are built within native houses and where, in the absence of light, species of anophelines have adapted themselves. In Palestine and Maccdonia they have been found to be the main breeding-place of A. claviger (bifurcatus).

Oil.—Oiling kills mosquito larve probably in several ways, but mainly by suffocation and its toxic action. The rapidity with which larve die depends upon the volatility and toxicity of the oil. The oil enters the spiracles of the larvæ as they break through the oil film, in order to reach the air and penetrate to varying distances according to the amount which When the tracheæ are full of oil death occurs within twentyfour hours. The main determining factor is the presence of toxic substances, such as aromatics present in the oil (Jones, 1951). Its spreading power can be improved by the addition of 1-21 per cent. of castor or coconut oil. In Palestine Kligler found the most effective mixture to be 1 part of crude oil to 4 parts of kerosene, with the addition of 0.1-0.2 per cent. castor oil. Anti-malarial oil (A.M.M.) is a mixture containing diesel oil, solar oil and kerosene put up by the Asiatic Petroleum Co. Diesel oil is unrefined, and is added to give a lasting effect. Maluriol is an approved mixture of petroleum impregnated with DDT to 5 per cent. (it is reasonable to expect now that all anti-larval oils should include DDT), with which a film is formed on the surface of the water. This is attained by allotting 2,750 sq. ft. to the gallon. By spraying the banks with this substance the grass may be destroyed, so that side pools and seepage are exposed. Waste motor oil has been used extensively in America. Pesterine is another mixture of oils, prepared by the Burmah Shell Oil Co. Liquid paraffin has been used by Swellengrebel and others in Holland. almost colourless oil, it costs about £1 per cwt., and it is claimed that its effects are not vitiated by wind or rain, that it does not evaporate, is not toxic to fish, and that it does not prevent mosquitoes from ovi-positing.

The following conditions are postulated for anti-larval oils as far as film stability is concerned:

- (1) The main point should be quick penetration of the respiratory siphons of the larvæ—in not more than ten minutes.
- (2) The oil should exert a direct toxic action on the larvæ and should change the flora of the streams.

The oil may be applied to the water in several ways. Spraying consists of forcing the oil under pressure through an atomizing nozzle from a special machine. Of the various patterns, the "Kent" sprayer best suits

the capacities of the tropical labourer. Sprayers should be fitted with leather or flexible metal adjustments, as petroleum oil perishes rubber in a few days. For road-side ditches oil carts may be used, but for all purposes the knapsack sprayer is the most adaptable. The best oil for the purpose is a heavy oil which will issue from the sprayer as a fine cloud and spread uniformly over the water. Oil swabs, or cotton-wool steeped in oil and weighted down by a stone, when thrown into water are ideal for rock springs and running streams. In certain malarial districts in the United States oil-soaked sawdust has been found to give a more complete and permanent oiled surface and has the advantage of being casily transported. The oil gradually exudes and spreads as an even film over the surface of the water. In Panama drip cans and barrels are used from which the oil constantly drips from cork wicks or through holes from which nails project, but their value as an oiling agent is less than that of sprays. Oil must be applied at seven-day intervals.

Paris green is copper aceto-arsenite and, in the quantities used for antimosquito work, is harmless to other forms of life; the particles are eaten by the anopheline larvæ and act as a direct poison; culicine larvæ are not affected in the same manner as the surface-feeding anophelines; fish are not killed. The powder should be intimately mixed with one hundred times its weight of finely-sifted dry road-dust, talc powder, soapstone or powdered charcoal, and sown by hand, down wind, over the water at the rate of 170 grains of Paris green per ten square feet of water surface. It is estimated that 1 kilo of Paris green is necessary for every 2½ acres. For rice fields a mixture containing 1-5 per cent. of poison is suitable. length of time the particles remain affoat depends upon the surface tension, and the more plentiful the vegetation the greater this is. In America (Western Tennessee and Northern Alabama), dusting machines have been invented for this purpose, and in large marshes the services of aeroplanes have been called on; they fly at a speed of 60 miles an hour and at a height of 25-200 ft. One plane can cover 20 square miles a day with this substance, and an automatic distributing machine is now used. The water current effectually aids in spreading the dust in a canal up to 3 ft. deep. Paris green was the principal larvicide used in the successful campaign against A. gambiæ in Brazil.

Greenglide, a preparation made by Craven & Co., Evesham, has an advantage over crude Paris green in that it will float for weeks. Its composition is:

Copper sulphate is especially useful in tanks where water is stored for drinking purposes and where sheets of algae are sheltering larvae. Its action is not direct upon the larvae themselves, but is one of starvation by killing off their food supply.

The prevention of mosquito breeding in uncovered and unscreened wells has peculiar difficulties. Oiling water with petroleum is apt to mar its taste. Williamson has recommended the liberation of gases and vapours.

Paraformal (3 oz. per square yard) vaporized at the bottom of a three-foot shaft will kill anopheline larvæ in half an hour. Sulphur dioxide acts by acidifying the water. When using gases, wells should be closed, and for this purpose a portable parachute to be lowered into them has been devised. For anti-mosquito measures with insecticides, see p. 861.

Larrivorous fish of some suitable local or well-known foreign species can be introduced. Favourites are the "millions" ("Millions-fish"—Lebistes reticulatus of the Indies), or "top minnow," Gambusia, which is a surface feeder, capable of withstanding heat and cold, and also viviparous and cannibalistic. In pools, weeds must be cut away to give the fish access to the larvæ. This method is efficacious in temple wells and pools in

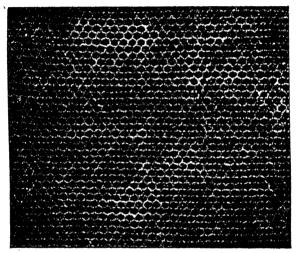


Fig. 10.—Mosquito-netting, 25/26 holes to the sq. inch. (MacArthur, Jl. R.A.M.C.)

Bombay against A. stephensi, and in the Adriatic Islands against A. maculipennis. In Java, by the introduction of a fish (Puntius javanicus) which feeds on water-plants, the breeding of anopheline larvæ is frustrated.

Mosquito-netting.—Mosquito-netting should contain 25 to 26 holes to the square inch (Fig. 10). The best is known as "bobbin" netting, woven of 30's cotton (by which is meant that 1 lb. of the thread will reach 30 times round a circumference of 840 yards). The square inch of the trade does not correspond to that of the mathematician; it means that the count is made along two lines of holes which fall within the opening of one inch square. Therefore, there are some 150 holes to the square inch (Fig. 11).

The main points in efficiency are that the holes should not be too large; that the net should not be so narrow as to permit knees and elbows to be bitten through the netting, and that the sides should be deep enough to be tucked in securely. When two single beds are used occupants can be protected efficiently as follows:—The beds are placed close together and the intervening space

covered with a single sheet, placed immediately over the mattress and beneath the other two sheets. The net itself should be suspended from the framework, or attached by tapes to rings hung on three wires and stretched across the room. When a mosquito is found inside the net it can be destroyed with ease by passing a lighted candle downwards about three inches from the insect when it will fly back into the flame. If the edges of the net are not tucked in, they must be so weighted that they touch the floor, so that the insects cannot crawl underneath.

During the daytime the net should be rolled up so that it contains no mosquitoes when set up for the night. Light attracts mosquitoes; for this reason blinds should be drawn down before turning on the light.

Application of dimethyl phthalate to wide-mesh nets.—The aperture may be $\frac{1}{2}$ inch square and easily penetrable by mosquitoes; but, if netting is impregnated with this repellent it will exclude the pests.

Screening of houses and barracks and other institutions by wire gauze is widely practised, especially by the Americans in Panama. The windows and doors are covered with wire gauze of a mesh fine enough to exclude mosquitoes; 14 mesh screencloth of 30 I.S.W.G. will suffice in most

districts, but for A. minimus a 16 mesh of 28 I.S.W.G. is necessary. In the former case the wire is 0.0124 in. in diameter and the aperture measures 0.059 in. Of the various metals used in the manufacture of screencloth, an alloy called Monel metal is the best and does not corrode in a damp climate. It is expensive and almost twice as dear as copper. The doors must open outwards or mosquitoes which have settled on the screens will be drawn into the house by anyone entering, and the screening must fit and be maintained so.

Mosquito boots of soft leather or canvas—or Wellington boots—protect the ankles and legs in the evening; for ladies, a pillow-case drawn up over the legs and feet is a useful precaution. Anti-mosquito veils and gloves (or gauntlets with sleeves) are used to protect soldiers and others on night duty.

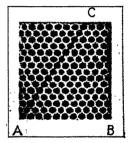


Fig. 11.—The correct method of counting the mesh of cotton netting. The mesh of this net is the sum of the counts made along the lines A B and A C, the hole at A being counted twice. (MacArthur, Jl. R.A. M.C.)

For application of DDT to malaria control, see pp. 862-864.

REFELLENTS.—Earlier repellents to which objections were raised have been replaced by a mixture of synthetic substances such as Indalone, 20 parts, Rutger's 612, 20 parts, and dimethyl phthalate, 60 parts. The issue is 2 oz. weekly for each man. During a shortage of other constituents (D.M.P.), dimethyl phthalate, gives the best results (Sketofax, B. W. & Co.'s proprietary preparation, is also based on D.M.P., as is also Dimeepol which contains, besides D.M.P., ethylhexandiol emulsified in a vanishing cream). During the hours of darkness the face and hands should be treated, but it should be kept out of the eyes. During the daytime it is necessary to repeat the application two-hourly. Where mosquito nets cannot be used, repellent fluid is used to impregnate headveils, sleeves and oversocks. These overgarments are made of fine string "fishnetting" which acts as a vehicle for the repellent. The impregnated netting is carried in a waterproof wallet with a cloth lining and re-impregnation is effected

by soaking the cloth-lining once a week with 4 oz. of repellent lotion. One drawback is its solvent action on plastics, especially artificial silk. Dibutylphthalate is similar, more persistent, but is less rapid in action.

Stearin cream gives 97 per cent. protection for eight hours. It is not greasy,

but unstable.

Stearin					•		. 16	per	cent.
Water							. 69	,,	,,
Glycerin							. 4	,,	"
33 per cent	t. am	noni	ı in w	ater			. 0.9	,,	,,
Prvethrum extract 2% total pyrethrins							. 10	• • •	17

PROPHYLAXIS OF MALARIA

The following terms must be defined:

- (a) Gametocyte prophylaxis.—Prevention of infection by the mosquito on account of the action of drugs on the gametocytes or their precursors in the human body.
- (b) Causal prophylaxis.—Prevention of infection by human host through the action of drugs on the sporozoites or upon intermediate stages of the malaria parasites in the body.
- (c) Suppressive prophylaxis.—Prevention of development of clinical manifestations of sub-patent infections by means of the action of drugs on the asexual forms.

Chemoprophylaxis.—Quinine prophylaxis has been practised by most residents in tropical countries for many years, but it has always been an open question whether its protective value had been definitely proved.

Experimental evidence is rather puzzling. Yorke and Macfie showed that sporozoites, injected by an infected mosquito, remain unharmed, even when the subjects are taking 30 gr. of quinine daily. Mühlens and Kirschbaum mixed malaria blood with a 1:10,000 quinine solution (left in contact for 12 hours) and were still able to infect a volunteer by inoculation and, moreover, Anopheles maculipennis developed occysts after feeding on a malaria patient on full quinine dosage.

Eight to ten grains of quinine hydrochloride were taken at sundown, two hours before retiring, during the malaria season. Kock's system was 15 gr. twice weekly, or on two consecutive days at the week-end.

Paludrine (prognanil) appears to be a good causal prophylactic in that it does not prevent penetration of sporozoites into the skin, but destroys the pre-erythrocytic stages (E.E. forms) of the malaria parasites. It is, moreover, non-toxic. The dosage is 0-1 grm. daily for 10 days. It is also an efficient suppressive chemo-prophylactic in as low a dose as 0-1 grm. daily. The earlier statements that one tablet once or twice weekly was sufficient have proved too optimistic, especially in West and East Africa. Daily dosage appears essential. It is more effective in subtertian than in benign tertian and prospective travellers should take 0-1 grm. paludrine for at least 10 days before entering a malarious country.

Daraprim (pyrimethamine), given weekly in a dosage of 25 mgm., afforded complete protection against overt malarial attack in a group of 14 non-immune subjects repeatedly exposed to mosquito infection (A. stephensi) by a West African strain of P. falciparum. The action appears

to be that of a true causal prophylactic against this species of parasite. The advantages are self-evident, though the belief that such small doses can produce such absolute protection would appear at present over-optimistic (Covell, Shute and Maryon, 1953).

Chloroquine diphosphate (aralen), which is devoid of toxic properties, and apparently has few side effects, is now being extensively used by American troops and by civilians in West Africa. As a causal prophylactic one tablet of 0.25 grm. taken twice weekly suffices. At the present time there are few statistics on this subject.

Primaquine (S.N. 13,272), an 8-aminoquinoline allied to pentaquine, is now under trial in American troops in Korea as a causal prophylactic and as a suppressant and can be combined with quinine. It has been tested out in Nicaragua and army hospitals in U.S.A. (Edgcomb *et al* 1950).

Atebrin (mepacrine).—It acts more as a suppressive than as a causal prophylactic. For the latter, in order to be completely effective, the dosage ranges from 6–8 grm. given over a period of 22 days before, and some 30–60 days after, exposure to infection. Encouraged by the many reports upon the atebrin method of suppressing clinical malaria in Malaya and elsewhere, Bryant, Hill and others in West Africa (1942) first advocated daily doses of 0·1 grm. on six days a week (Sundays excepted); ill effects were not noted and the protection afforded, especially against subtertian malaria, was most satisfactory. This was also shown in the surprisingly low incidence of blackwater fever. It was recommended that atebrin prophylaxis should be instituted at least one week before entering the endemic area and continued for one month after leaving for Europe.

The important factor in causal and suppressive prophylaxis is the atebrin level of the blood. To be effective this should be between 25–30 mgm. (γ) (or 0.001 grm.) per litre of plasma, or 2.3–3 γ per 100 ml. (25 ml. of blood are required for the test). Under active service conditions in troops, this level is much influenced by sweating or by too rapid elimination in the urine. It seems that when once this level has been lowered, malarial infection can break through and parasites may appear in the blood in large numbers, but if atebrin is then given in therapeutic doses (0.6 grm. initial dose, followed by 0.3 grm. daily), the trophozoites once more disappear.

GENERAL CONSIDERATIONS OF DRUG PROPHYLAXIS

Clark and his colleagues, as the result of ten years' experience of drug (atebrin) prophylaxis in Panama, concluded that even when it is given to all persons found infected at monthly surveys, it is impossible to eradicate malaria parasites entirely, when large numbers of anophelines are present, but severe clinical malaria can be eliminated. Field and Niven, on the other hand, have remarked upon the rapid reappearance of clinical malaria after the suspension of drug chemoprophylaxis and concluded that effective drug prophylaxis is not consistent with the acquisition of effective immunity. The chemoprophylaxis of blackwater fever is identical with that for malaria.

Inoculated or therapeutic malaria.—Following the work of Wagner-Jauregg of Vienna, the treatment of general paralysis of the insane and other grave nervous disorders includes the injection, subcutaneously or intramuscularly, of 1 to 2 ml. of blood containing benign tertian parasites, with consequent production of attacks of malaria in the person thus injected. The best results are obtained with blood which has been immediately defibrinated and kept in a thermos flask at freezing-point. It is most important that P. vienta and P. ovale strains should be used: deaths have occurred from inoculation with certain strains of P. falciparum, though others in James's hands have proved beneficial. Favourable results have been recorded in Vienna from the employ-

ment of Spirochata duttoni of relapsing fever in place of malaria.

Therapeutic malaria may also be produced by the bite of an infected mosquito or by the actual subcutaneous injection of the extract of the salivary glands containing sporozoites. Contrary to the opinion formerly held, it has been shown that inoculation of sporozoites from the salivary glands of one infected anopheles will produce in some persons quotidian rigors due to parasites sporulating within a day of each other. In many cases, also, after an incubation period of 7-10 days, the onset of the malaria attacks is characterized, not by typical intermittent fever, as seen in Charts 1, 2, but by a remittent fever which may persist for a week or more before becoming frankly intermittent (Chart 5). This feature appears to have been noted in the historic inoculation experiments originally carried out by Manson and Grassi. Kitchen and Putnam (1946) describe the onset as characterized by a few days of continuous-remittent fever, quotidian or tertian intermittent, or by a combination of both. Regardless of type of onset most P. vivax attacks commence and continue with quotidian periodicity. One objection to the use of benign tertian malaria is proclivity to quotidian fever, which is extremely exhausting to debilitated patients. Injections of thic-bismol, 0.2 grm., have been shown by a number of observers (Schwartz, Brunsting and Love, Cole, Whelen, and Shute) to have the property of destroying the half-mature schizonts of P. vivax, thus climinating alternate cycles, and of transforming a quotidian into a tertian fever. (Thio-bismel is the trisodium salt of bismuth thio-glycollic acid—Bi (SCH2 COO Na)3—and contains 38 per cent. metallic bismuth.) The optimum time for injections is about the fourth day. During the incubation period it has no effect; a similar effect has been shown on quartan by Kaplan (1946). The results of therapoutic malarial treatment have, according to Yorke and Macfie, been favourable: 27.4 per cent. of general paralytics were regarded as temporarily cured, while in a further 20.2 per cent. great physical and distinct mental improvement was observed. It has been proved that stabilization takes place so that re-adaptation to family life and social responsibilities is possible. In other forms of cerebro-spinal syphilis, it seems as if malaria therapy acts as a mordant for specific medication.

Shute has maintained a Madagascar strain of P. vivax through mun and mosquito over a period of 21 years. The number of anopheles infected was

24,361 and patients infected 1,739 over eight years.

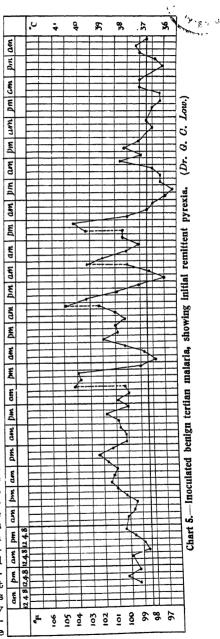
In inoculated infections disinfection by quinine, paludrine or atebrin is extraordinarily easy. To effect a complete cure, the amount of quinine administered varies from 45–150 gr. and about 3 grm. of atebrin. Relapses after subcutaneous inoculation with B.T. quartan or ovale after treatment are almost unknown, while in naturally-acquired malaria they are common. It seems, therefore, that malarial infection produced by the injection of sporozoites is much more long-lived and much less amenable to quinine and can now be explained by the existence of E.E. forms in the liver. Valuable information about the failure of quinine to act prophylactically has also been obtained. The

¹ Injections of neoarsphenamine have a similar effect.

administration of quinine in 10 gr. solution daily for five days before, on the day of, and eight days after the bite of infective mosquitoes fails to § prevent the development of malaria; similar results have been obtained in cases where 30 gr. in solution were given on the day of feeding infective mosquitoes and on each of the two following days. These experiments show that quinine has no action upon sporozoites injected by the mosquito, and they remain virile after immersion in quinine suspensions 1: 2.500 for four hours; on the other hand the development of malaria can be prevented by 10 gr. of quinine daily taken for ten days after the infecting bites, but this does not prevent long-term relapses.

Nephrosis treated by malaria.—The effect of inoculated malaria on nephrosis is essentially the same as that of A.C.T.H. Nephrosis, in its earlier stages, may be reversed by these means. In one instance A.C.T.H. did not provoke a remission, although malaria subsequently did. Lipoid nephrosis is also favourably influenced and the ædema is cleared up by diuresis (Gairdner and Byrne, 1952).

Artificial infection of susceptible species of anophelines, and technique employed.—For the production by mosquito bite of malaria infection in general paralytics wildcaught mosquitoes obtained in country districts free from malaria may be used, but it is now usual to breed them in insectaries, allowing them to obtain blood meals from guinea-pigs. insects are collected one by one in a test-tube and transferred to a mos-When about 300 have quito cage. been caught, a waterproof cover is drawn over the cage, which is then taken to the laboratory. After removal of the cover, the cage is placed in an incubator at 23° C. for twentyfour to forty-eight hours in order that blood in the stomachsofthemosquitoes may be digested quickly and that they may be ready to feed upon the in-It is essential that the fecting case. peripheral blood should contain male



and female gametocytes in the ripe stage; the male forms should "flagellate" readily in a moist-chamber preparation of freshly-drawn blood (see p. 1076).

In artificially-inoculated malaria cases, in order to produce, for example, a sufficient number of gametocytes of benign tertian, James found it best to permit the patient to have a number of (ten or more) attacks of malaria before administering a small dose (5 gr.) of quinine. A remission of fourteen to seventeen days will occur before the next attack, when gametocytes in the right stage should be abundant in the peripheral blood. When it has been determined that gametocytes in the blood are sufficiently numerous and ripe to ensure infection in the mosquitoes (not less than 20 male and female parasites per c.mm. of blood for P. vivax: 50 or more for P. falciparum) the mosquitoes, empty of blood, are collected in large cages and transferred to glass feeding jars (50 in each). The malaria-stricken patient is laid flat on his back and a hot water bottle is placed against his thigh which encourages the mosquitoes to feed. Four to five feeding jars are held in position against the leg of the patient for twenty minutes to half an hour. The jars of mosquitoes are immediately taken to a heated laboratory at 25° C. The mosquitoes are then released from jars into a small cage measuring 1 ft. (30 cm.) cube. By the aid of artificial light those mosquitoes filled with bright red blood are transferred to a large cage. The following day 2-3 are dissected, blood smears are made from the blood clot and a search is made for oökinetes. Blood films are taken and kept in a moist chamber for fifteen minutes to enable male gametocytes to be tested for "ripeness" and fertilization of female gametocytes to take place. From the third day after the batch has fed the stomachs of a few mosquitoes are dissected daily till the oocysts rupture and sporozoites are found in the salivary glands.

In the case of P. vivax the number of female gametocytes required to produce infection in A.m. atroparvus is between 6-12 per c.mm. of blood, but in order to produce a reasonable infected batch, 100-200 ripe gametocytes per c.mm. are necessary. Many more gametocytes may be present and as many as 1,000 occysts may be found in the gut of one mosquito. As each oocyst may contain as many as 1,000 sporozoites, such a mosquito may contain as many as one million sporozoites in its tissues. In primary cases of P. vivax malaria gametocytes are seldom found until the seventh day of the attack and reach their maximum between the tenth and fourteenth days. The optimum temperature for development of P. vivax in the mosquito is between 23° C. and 25° C. and the minimum is 16° C.

when the cycle takes thirty days.

Mosquitoes which are infected with hundreds of oocysts retain their ability to transmit malaria for at least one month (Shute).

CHAPTER V

HUMAN TRYPANOSOMIASIS

Definition.—Diseases produced by parasites of the genus *Trypanosoma*, characterized by irregular and chronic fever, skin eruptions, local ædema, adenitis, physical and mental lethargy, and sometimes death. The trypanosome is spread by the tsetse flies (*Glossina*) in Africa, and by winged bugs (*Reduviidæ*) in Central America.

The trypanosomes are blood parasites which are widely distributed in animals, especially in big game, in the countries in which these diseases occur. These animal hosts act as reservoirs of the trypanosomes which cause disease in man. The geographical distribution of African human trypanosomiasis is shown in Map I; that of the South American in Map II.

I. AFRICAN HUMAN TRYPANOSOMIASIS

Geographical distribution (Map I)—The distribution of human trypanosomiasis (sleeping-sickness) corresponds roughly with that of the tsetse flies, Glossina palpalis, G. tachinoides and G. morsitans. It is found in scattered areas in French W. Africa, on the Gambia, in Sierra Leone, the Gold Coast, Nigeria, Cameroons, the Southern Sudan, and Uganda; but its main stronghold is along the waters of the Congo and its branches. The most southerly focus in Africa has been found in the Okavango and Chobe swamps in Ngamiland, on the borders of the South African Union. Rhodesian sleeping-sickness is mainly confined to East Africa. The following is a detailed summary of the known distribution:—

Distribution of Sleeping Sickness (Trypanosomiasis) in Africa

In French West Africa.—T. gambiense prevails. G. palpalis and G. tachinoides are vectors.

Senegal to 30 miles North of Dakar (Sangalkam).—In South Casamance, Siné-Saloum and on Minor Coast.

French Guinea.—Labé Mamou in Fouta Jalon and in forestal regions South and West of Kissidougou and North Guéckédou.

French Sudan.—Along Bani River. Smaller foci near Black Volta River, South of Bamako, along Niger and tributaries, Senegal River and tributaries.

Niger.—In extreme South on Niger River between Say and Boumba, district of Tamou.

Ivory Coast (Upper).—Ouagadougou, Koudougou, Yako, Bobo-Dioulasso, Banfora, Gaoua, Diebougou, Batié Kampta.

Ivory Coast (Lower).—Province of Man.

Dahomey.—Tanéka-Koko, Dompago, Djougou Division of Parakou Province.

Togo.—On border of Dahomey, North East of Sokodé.—Banks of Binah, Kara,
Pakélou. Poundja and Zinah Rivers.

Portuguese West Africa (Angola).—North districts of Zaire, Congo, Cuanza, and Lunda. Coastal districts at Benguela, Lobito, and Egito. G. morsitans found in East Angola.

Portuguese Guinea .- Mildly endemic, G. pulpalis and G. submorsitans

widespread.

Islands of San Thomé and Principé.—Introduced from Angola in 1907. Repressive measures—slaughter of wild pigs. In 1915 Principé free from trypanosomiasis.

Spanish Guinea.-Utamboni, Muni Rivers in South, Beni River in North,

Estuary of Benito River and Aye River.

Island of Fernando Po.—G. palpalis common. In 1919 try pomosomiasis was widespread.

Liberia.—In East Province between St. John and Sangwin River. In 1940 epidemic in Kissi tribes.

British West Africa

Gambia.—North Bank Province in Lower Baddilu area: South Bank Province—Bintang-Bwiam, Kanfinda-Sintet areas, also Bathurst, Kimbo St. Mary Province, MacCarthy Island, and Upper River Provinces. G. pulpalis, G. tachinoides and G. morsitans common.

Gold Coast.—Number of cases increased since 1925—favourable conditions produced by deforestation. Highest incidence—Kumasi, Beikwai, Yendi, Clambaga, and Navrongo.

In Northern Territories, in Burifoo, Nadawli, border area between Lawra and

Tumu, South Mamprussi, Kusasi and Kamba valleys.

Sierra Leone.—Endemic on Sherbro Island. Chief zone is Kailahun district in Kissi tribe.

Nigeria.—Infection rate 2-2 per cent. Central—Zaria, Niger Province, South part of Katsina and Kano, parts of Benue, Bauchi and Plateau Provinces. Recently South Division and Jemaa.

In North G. tachninoides; in South G. pulpalis, G. mursitans and G. submorsitans.

Cameroons (Mandated Territory).—Along tidal creeks, up Mongo River in the Tiko area. In Cameroon Mountains, 20-40 per cent. of natives infected.

French Cameroons.—Upper Nyong focus is cradle of disease. In West region two centres are Noun and Mungo.

French Equatorial Africa.—Well distributed; chief centre, Moyen Congo. Gabon.—In Estuare department S.S. has increased since 1933, especially at Libreville, also in districts of Nyanga, Ngounié, Woleu-N'-Tem, Ogooué-Maritime, Adoumas and Djouah.

Moyen-Congo.—Haute-Sangha near South East boundary—subdivision of Nola—most severely infected areas in Equatorial Africa—20 per cent. infected, also subdivision of Sibiti, in Niari and the Dongou subdivision in Lower Oubangui area.

Ubangi-Shari.—Ouham worst infected department, also Kemo-Gribingui. Foci also in Zémio and Obo in Haut M' Bomou, Lobaye, Ombella-Mpoko, Ouham-Pende, Ouaka, and Basse-Kotto.

Chad.—Moyen Chari along the main river in South West, in Niellim district, to North West in Logone, in subdivision of Moundou and Doba, in Baïbokoum, and focus in Kasser canton/between Fort Lamy and L. Chad.

Belgian Congo.—Uneven'in all provinces. Large areas free in centre North and North East of Stanleyville, on Katanga plateau to the South. T. gambiense prevalent, but T. rhodesiense suspected in Bukania. In province of Léopoldville, along Congo to Kwa, along Kasai River, in Kwango to Moyen Wamba and East to Kwilu. Province of Lusambo vast endemic area. In Province of Coquilhatville S.S. is regressing, in Stanleyville stationary. Region of Lake

Albert has remained free from infection for five years. In Costermansville results of control favourable, but large foci still remain along Lualaba, and Kongo-Kindu railway. In Province of Elizabethville increase of endemicity on the Lualaba, but some regression on L. Tanganyika.

Ruanda-Urundi (Mandated Territory).—Notable regression in recent years. Infected areas confined to narrow strip below 11,000 metres along Ruzizi River, bordering the East shore of L. Tanganyika.

Anglo-Egyptian Sudan.—Confined to South district of Equatoria Province where G. palpalis fuscipes is found. Foci are Tembura in the Zande district of the Yubu River close to the West border of French Sudan. G. morsitans in Nuba Mountains, G. submorsitans and G. palpalis on Yubu and Sueh River.

British East Africa

Uganda.—S.S. appeared in epidemic form on shores and islands of Lake Victoria in 1900; reduced population of 300,000 to one third. Epidemic arrested by removal of population. In 1919 milder epidemic in Madi district of the Albert Nile and spread to West Nile district. Now West Nile and Koich River area chief focus. Minor foci in Gulu, Madi and Chua districts, and in Lake Edward-George area. In 1941 cases discovered at some distance from Lake Victoria, probably due to T. rhodesiense. In 1942 small epidemic in Busoga district spreading to Central district and across Kenya border. Buvuma Island South of Jinga also infected. Investigations suggest that here G. pallidipes is vector of T. rhodesiense. Other species G. palpalis, G. morsitans and G. fusca.

Kenya.—S.S. introduced from Islands of Lake Victoria and reached South Kavirondo in 1906. Now found in Central and South Kavirondo districts of Nyanza Province, mostly in Kadimu, Uyoma, Semie, Port Victoria and Kaniadoto. T. gambiense chief parasite, G. palpalis, chief vector, also G. swynnertoni. In South Kavirondo G. brevipalpis and G. pallidipes.

Tanganyika Territory.—Up to 1922 T. gambiense was trypanosome recognized and G. palpalis vector. From that time Rhodesian type recognized East of Mwanza where G. morsitans and G. swynnertoni abound. 1938–1940 increasing number of cases in North Province. At present S.S. found—Central Province—Singida; East Province—Ulanga; Lake Province—Mwanza, Musoma, Biharamulo; South Province—Liwale, Masasi, Tunduru, Songea; West Province—Kahama, Tabora, Kigoma, Ufipa; South Highlands Province—Chunya. Eleven fly-belts are recognized. Great Western belt extending North West to Uganda border and South West to South end of Lake Tanganyika; Great East belt passing to Portuguese East Africa and North to Kenya. G. morsitans found in half the territory. G. swynnertoni in North zone in thorn woodland. G. pallidipes widely dispersed in pockets.

Nyasaland.—In view of numbers of tsetse small numbers of cases of S.S. surprising. Infected areas in Kota Kota in South Nyasa. G. morsitans widespread. Trypanosome is T. rhodesiense of reduced virulence.

North Rhodesia.—In North trypanosome is T. gambiense conveyed by G. palpalis. In South it is acute Rhodesian type—T. rhodesiense conveyed by G. morsitans. Increase in 1935 near Mumbwa to West of Livingstone-Broken Hill Railway. Luangwa Valley constitutes endemic focus. Gambian form in the extreme North in Abercorn district, near shores of Lake Tanganyika, mainly in village of Mbete.

South Rhodesia.—T. rhodesiense S.S. near Busi River in Sebungwe district. In 1942 cases discovered near Chirunde on the Zambesi River in the Lomagundi fly-belt. Main tsetse in G. morsitans.

South Africa—Bechvanaland Protectorate.—In Ngamiland in North S.S. (local name Kgotsela) known since 1908. Tsetse belt in Okavange and Chobe swamps. Trypanosome—T. rhodesiense and G. morsilans vector. Now chief focus is Tsau-Gwedau area.

Portuguese East Africa—Mozambique.—S.S. due to T. rhodesiense on shores of Lake Nyasa. G. morsitans, vector, is widespread over area bounded by Lake Nyasa in West, Rovuma River in North, and Lucholingo River in South East. In South Catur and Madimba.

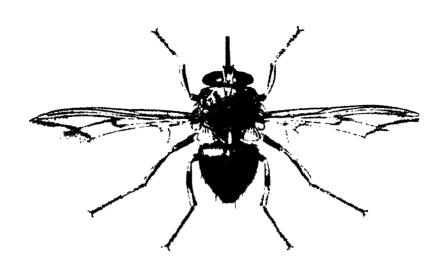
Abyssinia.—S.S. thought to exist in low country South and West of Addis Ababa. G. palpalis and G. morsitans occur along tributaries of Acobo and Chibise Rivers. G. pallidipes also.

GAMBIENSE SLEEPING SICKNESS

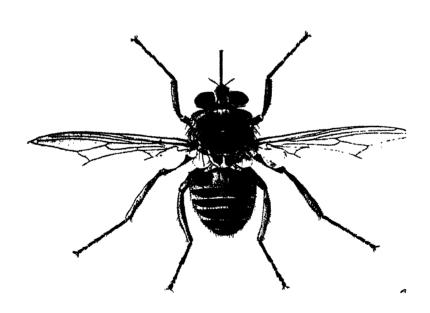
Ætiology.—Neither age, sex, occupation, nor race per se has any influence on the susceptibility to trypanosome infection, except in so far as those factors conduce to opportunity. Thus, Schwetz found a baby of twenty days old infected in the Belgian Congo. Occupation (boatmen, fishermen, water-carriers) conduces to infection, if it entails frequenting the waterside haunts of the glossina. In common with other trypanosomes, T. gambiense (Fig. 12), as seen in fresh blood, is an active, wriggling organism, having a spindle-shaped body which is slightly compressed laterally and spirally twisted. Dividing forms are sometimes met.

There is no uniformity in the number of parasites in the blood; sometimes they are fairly abundant, one or two in each field of the microscope; at other times, and in the same patient, it may be difficult or impossible, even after prolonged search, to find a single specimen; in some instances they tend to recur cyclically at intervals of a week or more. On the whole, although with exceptions, the parasites are most abundant in the blood during the febrile attacks. Apparently the blood is not their only or their principal habitat. They are usually found easily in enlarged lymphatic glands, and have been seen also in the cerebro-spinal fluid, serous cavities, and in the substance of the solid organs, including the brain, where they are distributed throughout the tissues outside the blood-vessels.

The parasite may be cultured on N.N.N., or better still the Razgha-Reichenow medium. Reichenow (1940) produced a culture in which 70 per cent. had lost their blepharoplast after treatment with trypflavin, but all the survivors retained this structure suggesting that it may be necessary for cyclical transmission. The trypanosomes are maintained in culture at a relatively low temperature for several months, but development does not proceed beyond a stage similar to that in the proventriculus of the tsetse when they are not infective to animals. Developing hens eggs have been used as a medium with some success. It can usually be inoculated into most mammals, including all the ordinary domestic and laboratory animals, and is especially pathogenic for the rat, but shows considerable variations in virulence. Monkeys, especially Erythrocebus patas, and dogs are susceptible, while amphibia and reptiles are immune. Inoculation of susceptible animals may be used to demonstrate the parasites when they occur in very scanty numbers in the peripheral blood, and is sometimes successful in those rare cases where they cannot be found after careful microscopical examination.



Glossina brevipalpis Newstead. 9 - 45 (From Austen)

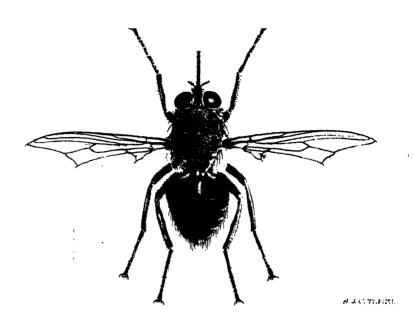


Glossina tachinoides Westwood. 9×6 (From Austen)

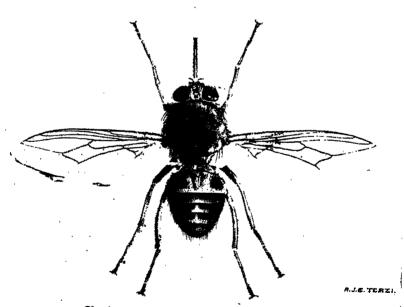
TSETSE-FLIES

(By permission of the British Museum (Natural History))

PLATE IV



Glossina palpalis Robineau-Desvoidy $\beta \times \alpha$ (From Austen)



Glossina morsitans Westwood. 9 × 6 (From Austen)
TSETSE-FLIES

(By permission of the British Museum (Natural History)) PLATE V

As shown by Laveran and others, these trypanosomes undergo agglomeration, both in blood and in artificial cultures, when exposed to unfavourable biological conditions.

How long a trypanosome infection may persist in the human body has not

been definitely determined, but there is direct evidence that it may continue for many years. From what we know of the incubation period of sleeping-sickness, it is not improbable that this period may extend to seven years or longer.

Transmission.—T. gambiense is not usually transmitted hereditarily in human beings, although the organisms have been found in the placental blood of infected rats, as well as in the livers of their embryos, but as in malaria and kala-azar, intra-uterine congenital transmission has occasionally been noted, and in Germany there is a record of one case in a European child born in Hamburg (Mühlens).

In the French Congo, Darré and his colleagues recognized hereditary try-panosomiasis and demonstrated try-panosomes in the cerebro-spinal fluid of a child born of an infected mother. David and Pape (1942) described two cases in the French Cameroons where transplacental transmission was established, trypanosomes being found in the blood of the infants as well as in that from the umbilical cord.

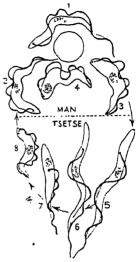


Fig. 12.—Life cycle of Trypanosoma yambiense and T. rhodesiense. (After C. A. Hoare.)

1—i. Trypanosomes in human blood (1, Long' slender form; 2. Intermediate form; 3. Short, stumpy form; 4. Stumpy form with posterior nucleus).

stumpy form; **. Standy form nucleus).

5—8. Stages in the tsetse fly (trypanosome forms 5, in stomach, and 6, in proventneulus; 7, Crithidia, and 8, Metacyclic trypanosomes in salivary glands).

Red blood-corpuscle drawn to scale.

Rôle of the tsetse fly as transmitting agent.—There is no evidence that biting flies other than the tsetse are concerned in the spread of human trypanosomiasis, but there are apparently two methods by which this fly is able to transmit trypanosomes: (1) cyclical, and (2) mechanical.

(1) Cyclical transmission.—As originally demonstrated by F. K. Kleine in 1909, T. gambiense undergoes an endogenous cycle of development in the circulating blood of the vertebrate. Certain short forms are regarded as the adult or metacyclic type, and they alone are responsible for carrying on the exogenous cycle. When ingested by the fly trypanosomes first multiply in the mid-gut; if the contents of the intestine at this stage are injected into the susceptible animal, they do not convey infection. After a cycle of development, lasting 12–20 days, the infective forms of trypanosomes congregate in the salivary glands. An important part is played by the peritrophic membrane lining the gut of the fly. (For further details, see p. 906.)

Cyclical transmission is influenced by the numbers of trypanosomes in the blood, by the host and by the blood plasma; it is diminished in chronic trypanosomiasis, in drug resistance and in exalted virulence of

T. gambiense.

There is no doubt now that transmission ordinarily occurs through the bite of infected flies, trypanosomes passing through the salivary duet as do the sporozoites of the malaria parasite. The adaptation of *T. gambiense* to *G. palpalis* is remarkably specific. In Western Nigeria and in certain districts of the Gold Coast, however, *Glossina tachinoides* is naturally infected and is mainly responsible for epidemies of sleeping-sickness in those countries. There is no evidence that the tsetse can transmit the trypanosome to its offspring.

Van Hoof, Henrard and Peel found that the index of cyclical transmissibility of trypanosomiasis on the Congo can be calculated by the

formula:

$$I = {g \over i} \times {n \times 100 \over N}$$
 where-

I = index of cyclical transmissibility.

q = number of glossina with trypanosomes in salivary glands.

i = number of glossina which after the fifteenth day of the experiment were found to harbour trypanosomes.

n = the total number of glossina found during the whole experiment.

N = number of glossina dissected during the experiment.

The mean index of transmissibility for the Congo is 3.63; the index of infectivity is 6.17, and the metacyclic index is 0.61 per cent.

(2) Mechanical transmission.—Duke, in Uganda, suggested on epidemiological grounds that mechanical transmission by glossina of a virulent strain of T. gambiense from man to man might be responsible for some epidemics.

Reservoir-hosts.—In the plateau province, Northern Nigeria, Taylor found that, in the absence of game and suitable aquatic reptiles, which form normal buffers, the fly feeds for the most part on man. Shade, which is only found near villages, is also important. These two factors combine to bring man and fly into close contact, and the rate of trypanosome infection of the fly is correspondingly high. In Uganda the same conditions obtain. Wild game may sometimes act as reservoirs. It has been proved that eleven common species of antelope (bushbuck, reedbuck, and waterbuck) can be inoculated with T. gambiense by subjecting them to the bites of experimentally-infected tsetse flies; furthermore, it has been established that certain marsh-haunting antelopes, especially the situtunga—Speke's antelope (Limnotragus spekei)—are commonly infected under natural conditions with T. gambiense. Thus, Duke found that they remained infected in the islands of Victoria Nyanza four and a half years after the evacuation of the human population.

Domestic stock must be now considered as a reservoir of infection for man, since T. gambiense has been found by various observers in oxen, goats and sheep. Van Hoof has stated that in the Belgian Congo domestic pigs form ideal reservoir-hosts, but show no obvious ill effects themselves; further that the strain remained infective to man after 10 transmissions

through those animals during the period of one year.

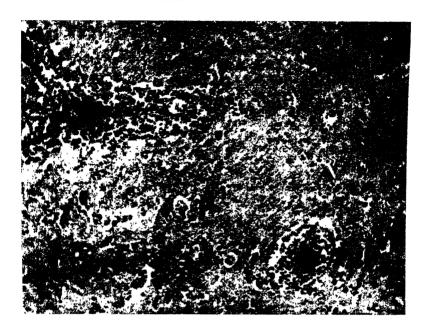


Fig. 13.—Section of brain in sleeping-sickness, showing round-cell infiltration filling perivascular spaces.

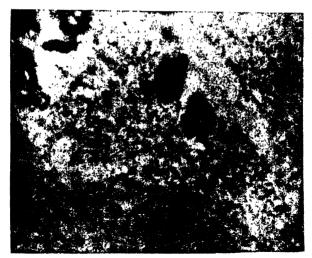


Fig. 14.—Photomicrograph of frontal lobe of brain in sleeping-sickness, showing trypanosomes in grey matter. (Dr. A. C. Stevenson, "Trans. Roy. Soc. Trop. Med. and Hyg.")

Pathology.—The chief lesions are in the lymphatic glands of the neck, submaxillary region and mesentery and in the central nervous system.

Central nervous system.—Typical pathological lesions are seen only when pathogenic trypanosomes have invaded the central nervous system. No gross lesions of the nerve centres are present, but there is progressive chronic leptomeningitis, especially in the Virchow-Robin space (where the pia runs alongside the blood-vessels and the fluid acts as lymph), and also on the vertex (Dürck's nodes).

The dura may be adherent to the skull and to the arachnoid. The brain itself is congested and cedematous, the surface smooth, with convolutions flattened by increased pressure. The consistency of the brain tissue is unaltered, except for softening around any hamorrhages that may occur. The ventricles are distended with fluid. In all cases there is perivascular lymphatic tissue (perivascular cuff) throughout the brain tissue and meninges, varying in amount and in different anatomical regions (Fig. 18). The invading cells are glia cells, lymphocytes, the morula (Mott) and Marshalko cells. The two latter types are degenerative plasmocytes. Morula cells stain deeply, with unilateral oval nucleus and vacuolated protoplasm. Marshalko cells are large plasma cells with a blue polar zone round the nucleus, with surrounding halo and acidophilic protoplasm.

As originally demonstrated by Wolbach in experimental animals and by Stevenson in man, in advanced cases, lesions in lymphatic glands and in brain are caused by invasion of the solid tissues by trypanosomes which have migrated from the bloodstream. In the brain they have been found mainly in the frontal lobe, pous and medulla, aggregated together in masses or nests without definite relation to blood-vessels. Myelin lesions of the brain have been described by Van Bogaert (1936) (Fig. 14). The organisms also invade the cerebro-spinal fluid; they enter the canal from the choroidal plexus where they congregate, as Peruzzi has shown, in active stages of division. Optic atrophy due to trypanosomiasis has been recorded.

The essential pathological features of cerebral trypanosomiasis recall a somewhat similar condition in general paralysis of the insane and disseminated sclerosis. Thus, the lumen of the vessels is contracted and the walls thickened. The cells of the spinal cord usually show fewer changes than those of the medulla or cortex. The endothelium of the capsules of the spinal ganglia is proliferated and there is infiltration of the trabeculæ with lymphocytes and plasma cells. The spinal canal may even be blocked by cell proliferation. The cerebro-spinal fluid in early cases is under increased pressure (80–100 cm. of water); the total proteins being very much increased, to 1 grm. per litre (normal 0·2 grm.).

The cells are increased to 15 to 500 or more per c.mm. (normal 2-3) and comprise lymphocytes, mononuclears, morula cells, eosinophiles and trypanosomes.

Kidneys.—There is glomerular nephritis, leading to fibrosis, also a generalized proliferation of the reticulo-endothelium in the capillaries.

Heart.—Ecchymoses and even large hæmorrhages in the epi- and endocardium have been observed. Peruzzi has shown (in the pathology of experimental trypanosomiasis in monkeys) that severe myocarditis is frequently present and is due to masses of trypanosomes within the muscle cells.

Liver.—There is spoiling of parenchyma cells, probably from toxic absorption, associated with depletion of the blood sugar.

Lungs.—These are characterized by intravascular proliferation of the reticulo-endothelium, which may block the capillaries with fibrosis, and collapse of the alveoli.

Bone marrow.—The fat is reduced and the whole tissue may be gelatinous and homogeneous.

Skin.—Localized cedema, due to collections of lymphocytes, is observed in the eyelids, perineum and skin of the back.

The spleen is slightly enlarged. The Malpighian bodies are few and inconspicuous. There is a general proliferation of the reticulo-endothelium, congestion at the periphery of the splenic sinuses, often focal necrosis with endothelial macrophages and ingested red blood corpuscles. Giant cells have been observed.

macrophages and ingested red blood corpuscles. Giant cells have been observed. Lymphatic tissue shows general hyperplasia. The glands are enlarged, soft and fusiform, with great proliferation of the lymphocytes. At first there is increase of large mononuclear cells, lymphocytes and later fibro lasts. They are very vascular, with small hamorrhages containing trypanosomes (which can therefore be easily demonstrated by gland puncture).

The blood shows definite anæmia due to toxæmia and erythrophagocytosis. The hæmoglobin is reduced and colour index below normal. There is usually auto-agglutination of red cells with rouleaux formation (cold agglutinins). The alkali reserve is diminished and blood sugar low.

Symptoms.—The incubation period of the glossina-conveyed disease and that resulting from direct artificial inoculation seem to be about the same, from two to three weeks in dogs, horses and monkeys. From experience of infected Europeans, in whom the dates can be controlled, it appears to be about fourteen days. The bite of an infected glossina is followed, in a proportion of cases, by local irritation of greater or lesser severity. This has been called the "trypanosome chancre" and is described as a red nodule surrounded by a white waxen zone. It subsides in a few days, to be followed, sooner or later, by fever, which may last a week or longer, and may be accompanied, in Europeans at all events. by a peculiar type of erythema and a certain amount of serous connective tissue infiltration (Plate VII, Fig. 1). The trypanosomes appear in the peripheral blood about twenty-one days after the infecting bite. A form of hyperæthesia, known as "Kerandel's sign," is usual, though not invariable; when the patient strikes any hard object he suffers discomfort amounting to actual pain after a slight delay. In time the fever subsides more or less completely, to recur at irregular intervals of days or weeks. It is sometimes mild, sometimes severe, and occasionally hyperpyrexial (106.6° F.), the evening temperature being always the highest. It may last for weeks and the apyrexial period may be equally prolonged, or it may be continuous. The fever and all other clinical manifestations of trypanosomiasis are irregular in intensity and duration. In time the patients become debilitated, anemic and feeble, both intellectually and physically. The spleen is usually enlarged. Severe temporal headache is very often present. The heart's action is generally rapid and easily excited and persistent tachycardia affords an excellent index to persistent infection. The cervical glands and those of other parts of the body cularge and may become tender. Only one gland may be visibly involved, or there

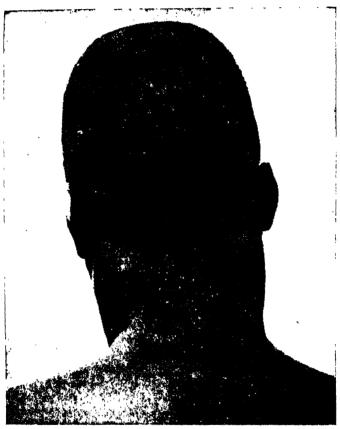


Fig. 15.—Enlargement of cervical lymph-glands in trypanosomiasis (Winterbottom's sign). (Dr. F. K. Kleine.)

may be polyadenitis, including the abdominal group. The implicated glands may be very prominent, or not easily felt, but are usually most conspicuous in the posterior triangle of the neck (Winterbottom's sign) (Fig. 15). In the early stage of the infection they are soft later indurated; sometimes they are painless, sometimes distinctly painful and tender, rarely suppurating. This condition of irregular fever, of debility, of polyadenitis, of slight anæmia, may go on for months, or even, in some instances, for years. At this stage there is usually insomnia and lack of concentration.

A proportion of cases may then terminate. Since this disease undergoes at various stages periods of quiescence, which may be very prolonged, it would be rash to call any instance of apparent recovery a radical cure. But experiments and observations by Laveran and others in other forms of trypanosome infection, as well as some cases in Europeans which have come under the Editor's notice, justify the belief that occasionally the parasite does die out spontaneously.

In a given area and in a given population there is a tendency for the virulence of the local trypanosome to decrease with lapse of time. Thus,



Fig. 16.—Trypanosomiasis rash in a European.

the trypanosome of the Gold Coast and Southern Nigeria, where sleeping-sickness presumably has long been endemic, is less virulent and much more amenable to treatment than that of Uganda, where it is of recent introduction; indeed the Editor, together with Cooke and Gregg, has described a series of particularly mild cases in Europeans from the Gold Coast in which trypanosomes were discovered during the course of routine blood examination, but the patients otherwise appeared normal, though one had a circular erythematous patch on the shoulder. Similar instances have been recorded by Lamborn, Howat, Davy, Sicé, Rolin and Mercier.

Remarkable features of human as well as of animal trypanosomiasis are skin affections and local edemas. In many of the lower animals infected by their special trypanosomes, papular and pustular eruptions are common, in addition to fever and physical lethargy; and in man, especially in negroes, an exceedingly itchy papular eruption is frequent. In the

European, and possibly in the negro—but in the latter, less evident on account of his colour—extensive skin areas are affected with a fugitive, patchy, frequently annular crythema (Fig. 16 and Plate VII, facing p. 246), usually most evident on the chest and back, but also very often on the face, legs, and elsewhere. This crythema seems to occur most frequently and most distinctly in the earlier stages of the infection. Some of the patches may be six inches or even a foot in diameter, their margins fading off insensibly into the surrounding normal skin. It usually takes the form of large rings, occasionally complete, more frequently interrupted and irregular. Sometimes it is confined to annular rings on the shoulders. Erythema nodosum sometimes occurs also. Pressure or any irritation of the skin gives rise at once to transient congestion from vasomotor paralysis of the skin capillaries. The rash can be brought out by heat, and especially by hot baths. Xeroderma and pruritus are often present in the terminal stages.

In some of the lower animals a usual feature is ordema of certain parts of the body, especially of the eyelids, the sheath of the penis, the undersurface of the abdomen, and the neck. Similar, though less extensive, cedemas occur in man, in whom they are most apparent in the face and about the site of the crythema. In many instances there is a general fullness of the features which, with concomitant flushing, is apt to convey

a false impression of sound health.

Neuralgic pains, cramps, formication, and parasthesiae of different kinds are not uncommon. Two of Manson's cases showed recurring orchitis, accompanied by an increase of parasites in the blood. Painful local inflammatory swellings, which after a time subside without suppuration, have been seen in some cases; periostitis of tibiae more rarely. Toxic iridocyclitis and choroiditis and doep cedema of the lower cyclid are sometimes met. The eye symptoms are not so evident in man as in the lower animals, interstitia keratitis in infected dogs being comparatively frequent.

Ridley (1945-1946) considers that intraocular infections are neither common nor important. In a series of 100 cases two only showed bilateral papillædema, there were four with indefinite disc edges and the presence of new connective tissue in the physiological cup and round the central

vessels. (Concurrent ocular onchocerciasis is common).

In most cases the spleen is enlarged, sometimes enormously, fluctuating with the fever, in the absence of concomitant malaria which, however, is a not infrequent complication. The liver may be similarly affected.

Although trypanosome infection is not, as a rule, transmitted to the feetus, the abortion-rate is increased from the normal 7 per cent. in Congo natives to 31.7 per cent., and the infant mortality-rate from 29 per cent. to 50 per cent. Trypanosomiasis in infants is extremely rare, though Kellersberger has recorded infection in one three weeks old.

Death from intercurrent disease, from rapid y developing cerebral implication causing convulsions, status epilepticus or coma may supervene at any stage of trypanosomiasis. Usually the case gradually drifts into the stage known as "sleeping-sickness." It is usually believed that the development of the sleeping-sickness stage in trypanosomiasis concurs with and depends on the entry of the parasite into the cerebro-spinal canal.

Sleeping-sickness stage (cerebral trypanosomiasis).—The terminal stage of trypanosome infection sometimes exhibits acute features, and sometimes is exceedingly chronic. While an interval of several years, possibly eight, may elapse from the commencement of the infection to the development of this terminal stage (Rodhain), in the majority of cases the progress is much more rapid. The characteristic terminal symptoms depend on implication of the nervous system, either by the parasite itself or by its toxins.

The average duration of this stage in the African is from four to eight months, not infrequently less; very chronic cases with a course of more



Fig. 17.—Cerebral trypanosomiasis. Appearance of patient in last stages of the disease. (Dr. F. K. Kleine.)

than a year are rare. Some observers refer to cases running on for three years or even longer, with occasional temporary ameliorations.

Generally, the first indications of the oncoming of sleeping-sickness are merely an accentuation of the debility and languor usually associated with trypanosome infection. There is disinclination to exertion; slow, shuffling gait; morose, mask-like vacant expression; relaxation of features; hanging of the lower lip; puffiness and drooping of the eyelids; tendency to lapse into sleep or a condition simulating sleep, somnolence or "near coma" during the day-time contrasting with restlessness at night: slowness in answering questions; shirking of the day's task. Dull headache is generally present. He will walk, if forced to do so, with unsteady and swaying gait. Later, there may be fibrillary twitching of muscles. especially of the tongue, and tremor of the hands, more rarely of the legs, indicating involvement of the motor centres. His speech is difficult to follow, becoming indistinct and staccato. By this time the patient has taken to bed, or he lies about in a corner of his hut, indifferent to everything going on around him, but still able to speak and take food if brought to him. He never spontaneously engages in conversation, or even asks for

food. As torpor deepens he forgets even to chew his food, falling asleen perhaps in the act of conveying it to his mouth, or with the half-masticated bolus still in his cheek. Nevertheless, such food as he can be persuaded to take is digested and assimilated. Consequently, if he is properly nursed, there may be no general wasting. So far the striking features are the mental and personal changes with a paucity of neurological signs. As time goes on, he begins to lose flesh, tremor of hands and tongue becomes more marked, and convulsive or choreic movements may occur in the limbs or in limited muscular areas. (Fig. 17.) Sometimes these convulsions are followed by local temporary paralysis. Sometimes, too, rigidity of the cervical muscles and retraction of the head occur. There is usually an intolerable pruritus of the skin; bedsores tend to form; the lips become swollen, and the saliva dribbles from the mouth. Gradually the lethargy deepens; the body wastes; the bedsores extend; the sphincters relax; and finally the patient dies comatose, or sinks from slowly advancing asthenia. Possibly he succumbs to convulsions, hyperpyrexia, pneumonia, dysentery or other intercurrent condition. Clinically, then, sleeping sickness reproduces the picture of a true encephalitis.

The manifestations described are subject to considerable variations. Thus, mania is not uncommon; delusions may present themselves, or psychical and physical symptoms not unlike those of general paralysis of the insane are developed. In the European, death is frequently due to convulsions, probably from the presence of the trypanosomes in the brain. Deep hyperæsthesia of the muscles is also quite common. The habits usually become bestial and he becomes a drooling, dribbling and drowsy idiot. Gelfand has drawn attention to transitory neurological signs, such as ptosis and ophthalmoplegia and transitory paralyses, such as facial palsy, meningitic symptoms, accompanied by papillædema and extensor

plantar responses.

During the whole course of the nervous stage of trypanosomiasis the other symptoms already described as characteristic of the infection may be in evidence. The knee-jerks, though lost towards the end, are active at first; the fundus oculi is usually normal; the sphincters, until towards the end, are controlled; the urine is normal, and the bowels, although generally tending to constipation, act with more or less regularity.

Trypanosomiasis in natives.—Lester recognizes three categories in Nigeria:—

- (1) Mild, with few symptoms, when equilibrium has been established between patient and parasite.
- (2) Involvement of the central nervous system—the commonest form.
- (3) Acute, leading to death before the central nervous system symptoms develop, toxemia being the salient feature.

Elsewhere the same three types are found, but the acute form predominates, especially in Tanganyika, where T. rhodesiense is the common parasite.

It is realized that, not only do the trypanosomes vary in virulence in different parts of Africa, but there is an almost equal diversity in the powers of resistance. Harding and Hutchinson (1948) have described an

outbreak in Fuero, Sierra Leone, where the majority of cases were symptomless without cervical adenitis, but with large numbers of parasites in the

peripheral blood.

In Central African natives symptoms of trypanosomiasis are considerably aggravated by, and in many cases mistaken for, those of other diseases. The patient is almost invariably infected with malaria, ancylostomiasis, schistosomiasis, and possibly filariasis, besides which much of the emaciation and the specific complications—septic rhinitis, otitis—are due to starvation and neglect.

Mortality.—Although spontaneous recovery may take place in the early stages of trypanosomiasis, it is believed that when the disease has arrived at the stage of sleeping-sickness, death is inevitable. Corré has told how native villages in Senegambia have been depopulated. What has occurred on the Congo, in Angola, and in Uganda, bears out this estimate of the gravity of the disease in epidemic form. Many islands in the Victoria Nyanza have been completely depopulated. The population of the implicated districts of Uganda, originally about 300,000, was reduced in six years to 100,000 by sleeping-sickness.

Immunity.—Man is immune to infection with the commoner trypanosomes of big game, T. congolense and T. vivax, and certain mammals are immune to trypanosomes which are pathogenic to others. Thus, T. vivax is pathogenic to horses and cattle, whilst rabbits, guinea-pigs, and mice are refractory. Although there is no direct evidence that man becomes immune after exposure to infection with T. gambiense, yet there is no doubt that when the disease has lasted any length of time in a district, as in Southern Nigeria, the inhabitants exhibit a degree of resistance not seen in districts more recently invaded.

The non-immune European generally suffers in a more acute form than does the Central African native under similar conditions. Russell and others who have studied the phenomena of immunity in man believe that the course of an infection with a pathogenic trypanosome depends upon the capacity of that organism to vary in a serological sense so often that it defeats possible variations in the host's defence.

Trypanocidal action of human serum on trypanosomes.—Following the interesting discovery by Laveran, in 1902, that normal human serum exerts a marked effect on the course of trypanosome infection in animals, a large amount of work has been devoted to this subject with the object of discovering an effective trypanocidal serum. Yorke, Adams and Murgatroyd have shown that normal human serum exerts a pronounced trypanocidal action in vitro at 37° C. on a number of strains of pathogenic trypanosomes, even when the serum is diluted 5,000-25,000 times; but in certain pathological conditions of the liver this power is lost entirely in vitro. The interesting fact has been observed that, in the sera of certain normal sheep and rabbits, an active trypanocidal substance exists which, when mixed with normal human serum, inhibits the trypanocidal action of the latter. A curious and almost inexplicable feature is the fact that T. rhodesiense, T. equiperdum and T. congolense are rapidly destroyed in vitro by this method, but T. gambiense is apparently unharmed. Possibly in this observation lies the explanation of man's immunity to infection with the pathogenic trypanosomes of cattle and other stock.

Diagnosis.—Chronic irregular fever, more especially if associated with enlarged cervical glands and, in the European, erythema multiforme, in a patient who has resided in tropical Africa at any time during the previous seven years, but especially recently, suggests a tentative diagnosis of trypanosomiasis and detailed examination with this possibility in view. Diseases with which trypanosomiasis might be confounded are malaria, kala-azar, pellagra, syphilis, leprosy, lymphadenoma (Pel-Ebstein disease), and, in its later stages, beriberi.

The diagnosis of trypanosomiasis is made absolute by blood examination. but the serum-formalin reaction (see p. 158) is usually positive in well-established cases and therefore may serve as a rough guide for differentiation from other African fevers on a large scale (Hope-Gill, Morrison, Dye and Cookson). and his collaborators have shown that there is a considerable diminution in the total serum proteins, and the loss is mainly due to decrease in scrum albumin. The ratio of serum albumin to globulin is always less than it is in normal persons. Davis, Broom and Brown have worked out a specific immunity reaction in trypanosomiasis known as the "adhesion phenomenon." This reaction is characterized by adhesion of blood platelets and cells to the parasite when acted upon by immune plasma in vitro. For this purpose trypanosomes, immune serum, complement and human cells are incubated together; if the serum is homologous the red cells become firmly adherent to the trypanosomes. Standard concentrations of red cells and trypanosomes are necessary to obtain constant results. Agglomeration and trypanolysis may take place, even if the red cells are unsuitable as indicators. This reaction is said to be specific for different species of trypanosome, and the immune body exhibits a high degree of thermostability. The test can be used in recognizing species of wild game which may act as reservoirs of T. gambiense.

In an endemic area Saunders found that 91 per cent. of proved human cases gave some degree of adhesion in this test, whilst 75 per cent. of controls gave none.

Saunders (1952) found 38 per cent of blood slides were positive in one thick drop. Trypanosomes are found most easily in fresh blood examined with $\frac{1}{6}$ in. (4 mm.) objective. For gland puncture needles should be of fairly wide bore; a convenient size (steel needle) is one of 0.8 mm. and a length of 2.5 cm. Drying the needle is essential. Lower cervical glands are more suitable than the higher. With the needle, at about 45 degrees to the skin, aim at the thickest part of the gland. Rotate the needle on its axis, push it in a little further and then withdraw it and pull out quickly. Examine smear with cover glass pressed down. The fluid consists of lymphocytes in a clear medium. Trypanosomes when seen behave like a small hooked trout kicking and thrashing amongst the lymph cells (McGowan).

Microscopical diagnosis of trypanosomiasis is sometimes difficult. Anæmia, as well as a relative increase of large mononuclear leucocytes, usually occurs. A well-stained blood preparation exhibits, even to the naked eye, a remarkable clumping of the red corpuscles (autoagglutination). As a rule, the parasites in the peripheral circulation are few, many fields having to be hunted before one is discovered. Sometimes none can be found; rarely are they abundant, as in the acute forms of T. rhodesiense.

The thick-drop method should always be employed and it is estimated that it takes 20 times as long to find them in thin as in *fresh* wet-drop preparations.

Blood centrifugation.—Take into a 10 ml. syringe 1 ml. of 6 per cent. sodium citrate in 0.9 saline. Fill the syringe with blood from a vein. Centrifuge for ten minutes on the low gear of the two-gear centrifuge. This brings the red cells down as a sediment, on the surface of which the leucocytes form a grey layer. Supernatant fluid is pipetted off into another tube. Examine the leucocyte layer and first sediment for trypanosomes. Re-spin supernatant in the high-speed gear for ten minutes and pipette off into a third tube. Examine the second sediment which occasionally reveals trypanosomes (in 16 per cent.). The third sediment similarly treated often has trypanosomes in 39 per cent. Sicé (1937) advised that the electric centrifuge should not exceed 3,000 r.p.m.

Greig and Gray, Dutton and Todd emphasized the value of lymph-gland puncture and examination of the aspirated lymph as the most certain method, particularly in the earlier stages of the disease, when the glands are soft before they have become sclerosed, and the trypanosomes abound in the lymph. This method succeeds in 87.7 per cent. of cases. ordinary hypodermic syringe needle suffices to aspirate a sufficiency of lymph. Massage of the gland assists the flow of lymph into the lumen of the needle (see p. 156). Gland-puncture should always be reinforced by the examination of thick blood-films. The glands may be unilateral or bilateral; sometimes they reach the size of a pigeon's egg and every gradation may be shown. Although the superficial glands may be easy to palpate, deeper ones may be more difficult. Three procedures for palpation are necessary: deep palpation, superficial palpation, and palpation by passing the palmar surface of the hand over the neck. The glands should have the consistency of a ripe plum. Harding and Hawking (1945) found both gland and blood examination positive in 30-40 per cent.; gland puncture positive, blood-film negative in 50-60 per cent.; bloodfilm positive, gland puncture negative in 10 per cent.

In the Belgian Congo (Foréami system) gland palpation is systematically performed by the European staff; microscopic examination of gland juice and blood by specially trained native assistants.

Hollins has demonstrated the value in diagnosis of a single method of estimating the 10-minute erythrocyte sedimentation rate. The "normal" African rate varies in different areas, but a pronounced fall in an abnormal rate after administration of antrypol is diagnostic.

Cerebro-spinal fluid, obtained by lumbar puncture and centrifuged, affords another (though not always a practicable) means of finding the parasite; according to Broden, parasites may be demonstrated in this manner in 4-5 per cent. of cases, but if the trypanosome is not found, suggestive information may be obtained from a lymphocyte-cell count of the fluid, as this may be increased to over 1,000 per c.mm. The globulin content of the fluid is also increased, but the colloidal gold curve is of the paretic type. With 4 ml. of fluid centrifuged trypanosomes are found in 0·15 per cent. of cases.

The diagnosis of trypanosomiasis is not justified on a cell count as low as 15 or 20. The limit should be about 30 cells. When present the morula cells of Mott are suggestive. The protein estimation appears to be open to the same objections as the cell count.

The importance of puncture of the cerebello-medullary space in the diagnosis was emphasized by Tajera. Suboccipital puncture through the occipito-atlantoid ligament into the cisterna cerebello-medullaris is simple and practically devoid of risk.

Le Port stated that the early changes in the choroidal plexus in trypanosomiasis are confined to the fourth ventricle, so that the immediate consequence is an interruption of the connections between the ventricles and the subarachnoid space. The only real orifices by which these two centres intercommunicate are by the foramina of Luschka, which lie between the cerebellar peduncles in the lateral angles of the fourth ventricle. These orifices are covered by the lateral choroidal plexuses of the ventricle. Obstruction of the foramina of Luschka results in separation of the subarachnoid space from the ventricles where the cerebro-spinal fluid is produced, and this causes automatically a state of disequilibrium of tension of the fluid between the two cavities. The intraventricular tension thus produced may give rise to a syndrome which is responsible for the signs of the first stage of sleeping-sickness. Intraventricular hypertension manifests itself by headache, nausea and a degree of somnolence.

Sicé has proved that the earliest reaction resulting from meningeal lesions is cellular; at first it is slight and unaccompanied by clinical signs; usually it progresses slowly, and the intensity of the meningeal lesions is shown by the number and character of the cells. The presence of leucocytes indicates that the lesions are active and, probably, recent. Plasma cells, dead cells and morula cells indicate older and more chronic lesions. As the cellular reaction develops, so the albumin content gradually increases. Prognosis can therefore be based upon the amount of albumin in the spinal fluid. Though this can be estimated by a number of different techniques, the proportion of the albumin and the globulin in the cerebro-spinal fluid is considered by most authorities to run parallel with the number of cells present.

Animal inoculation is used if the parasite is not found by blood or lymph examination, 2–10 ml. of the blood being drawn from a vein and injected. Of the ordinary laboratory animals, the most susceptible, and therefore most reliable, are the guinea-pig, the rat, the dog, and Macaca and Cercopitheous monkeys. Such inoculations are of value as a test of recovery, as well as for diagnosis. The best animals on the Gold Coast are the green cercopitheous monkey and the pouched rat—Cricetomys gambianus. Ten ml. of citrated blood are used for monkey, cat or dog; 3–6 ml. for Cricetomys and 1 ml. for a small rat. Interval between inoculation and appearance of trypanosomes in the peripheral blood varies from 6–49 days. Relapse can be produced by intraperitoneal injection of olive oil.

Sternal puncture has recently been introduced as a reliable and ready method of diagnosis. Guibert and Boscq found T. gambiense in the bone marrow of 29 out of 30 untreated cases, whilst Lenhard, Jospin and Gallais claim that it is superior to any other method.

The trypanosome is easily stained by most dyes, those in use for malaria work giving the best results. A $\frac{1}{6}$ -in. objective suffices to find the parasite.

Differential diagnosis.—Kala-azar and trypanosomiasis, especially in their earlier stages, may be difficult to differentiate, but enlarged glands, local cedema and erythema multiforme in trypanosomiasis, and their absence in kala-azar, suffice for distinction. Blood or gland-lymph examination, or, if this be negative, hepatic or splenic puncture, should establish the diagnosis.

General paralysis of the insane, cerebral tumour, forms of meningitis, especially encephalitis lethargica (often inaptly termed "sleepy sickness"), have features in common with trypanosomiasis and must be considered. The serum of some cases of trypanosomiasis has been said to give a positive Wassermann reaction, but this may be due to a co-existing syphilitic

infection.

TREATMENT

Especially in natives, preliminary treatment directed towards eliminating superimposed infections with ancylostomes or schistosomes is advisable, on account of damage to the liver-cells which renders toleration of arsenical drugs difficult.

1. Antrypol "Bayer 205," introduced in 1920, is valuable in eradicating

trypanosomiasis, especially in the early stages.

In artificially injected animals it is non-toxic. The dosis tolerata is estimated at 160 times the dosis therapeutica, injected intramuscularly or intravenously, being lethal to T. brucei, T. gambiense and T. rhodesiense and moreover it exerts a prophylactic action.

The average dose for man is 10 ml. of 10 per cent. solution in distilled water intravenously. The total amount to effect cure is 10 grm., though trypanosomes usually disappear after 5 grm. The dose should be repeated at weekly intervals.

In early infections the best and most lasting results are usually obtained by larger initial doses, such as 1 grm. on the first, third, tenth and thirteenth days. Sometimes doses of 1.5 to 2 grm. are given. Although it is most active in destroying trypanosomes in the blood it is incapable of doing so after they have entered the brain.

The value of antrypol lies in its power of rendering the trypanosomes fit for phagocytosis by the reticulo-endothelial cells—a kind of opsonizing effect. This action greatly enhances the effect in the living animal and thus explains its efficacy in vivo rather than in vitro. There are also good reasons for believing that its delayed action is due to combination with plasma and tissue proteins, so that serum, cerebro-spinal fluid and urine continue to exhibit subsequent trypanocidal action when injected into trypanosome-infected mice. Intrathecal injections are not recommended.

Immediately after the injection of the drug both the physical condition and mental outlook of the patient are improved. The drug is harmless to man, except that it has a cumulative action and is a kidney irritant, so that, after three or four injections, the urine contains albumin and small yellow, granular casts. This is the result of excretion via the urinary tubules, and lasts about six weeks. In some susceptible individuals toxic dermatitis—a red, itching and papular rash—develops, usually after the third injection. According to Corson, a painful condition of the feet, apparently peripheral neuritis, has sometimes been observed. A rare but disagreeable sequel is exfoliative dermatitis.

2. Tryparsamile.—Tryparsamide should not contain less than 25·1 per cent. of arsenic. "Fourneau 270" (Orsanine) is the French equivalent.

Tryparsamide, when injected, is quickly absorbed, either by the intramuscular or intravenous routes. The chemotherapeutic index—the ratio between the curative and maximum tolerated dose—is 1:2; for atoxyl it is 1:1.

Individual doses are large, varying from 1 to 4 grm. (the maximum is 60 mgm. per kg. body weight). The drug exerts a marked effect on symptoms, especially when the nervous system is involved. Its chief value lies in the case with which it penetrates into the cerebro-spinal fluid, where it eliminates the trypanosomes. The great reduction in the lymphocytes in the cerebro-spinal fluid in cerebral trypanosomiasis is attributed to its high power of penetration. In average cases the initial dose should be 1 grm. in 10 ml. of distilled water, subsequently 2 grm. three times weekly. A total dosage of 24 grm. is necessary.

In chronic cases the dosage may have to be as high as 70-80 grm, for permanent cure, according to Van den Branden, but in mild infections he obtained 57 per cent. apparent cures with a total of 20-60 grm., but in a smaller percentage when trypanosomes were present in the corebro-spinal fluid.

Fowler (1946) has given massive doses by the intravenous drip method in 42 cases. The simple apparatus consists of a glass container and rubber tubing, the interceptor being improvised by using an intravenous needle and the barrel of a glass urethral syringe. The dose is 2 grm. daily for 6-9 days, but a week's interval has to be interposed after 3-4 days owing to exhaustion produced by high fever during the injections.

The dose of tryparsamide was dissolved in two pints of sterile double-distilled water and given with a hypodermic needle at a rate of 40 drips per minute, allowing for two pints of solution in eight hours.

In the majority trypanosomes were present in the cerebro-spinal fluid. In three acuity of vision was affected and seven deaths were due to the febrile reaction induced, but the immediate results were good.

Chesterman concluded that, to be effective, solutions should not exceed 40 per cent. which is near saturation point. The water must not be alkaline which produces precipitation. Intramuscular injections are also efficacious, but this solution should not be stronger than 20 per cent.

Prolonged administration of maximum tolerated doses gives the best results. Children up to twelve years tolerate the drug well and may be given up to 20 mgm. per kg. body weight for 12 injections. If the drug is used in strengths of more than 20 per cent. by the intramuscular route induration or abscesses may result. Herxheimer reactions with acute mania have been recorded with excessive doses.

In advanced cases in adults the initial dose should be 20 mgm. per kg., on the fourth day 30 mgm. per kg., while on the eighth a course of 20 injections of 40 mgm. per kg. at four-day intervals should be commenced: after a three-months' interval a course of 10 injections should be repeated.

As evidence of cure, physical improvement and restoration of mental activity, together with a normal cell-count and albumin content of the cerebro-spinal fluid for one year should be taken into account.

An excess of albumin and increase of cells is sometimes noted for a short period, but may be only temporary.

Arsenic resistance.—This subject has been much debated. Van Hoof states that it is often difficult to create this in the laboratory, whilst routine treatment does not inevitably increase it in the case of a relapse; but in mass treatment (as in the Belgian Congo), where this resistance is on the increase in an endemic area, it is rather because the routine treatment has eliminated a large number of non-resistant strains from the trypanosome reservoir.

Non-resistant strains are usually more easily transmitted through the tsetse (see p. 126).

Results.—In early cases an apparent cure is almost invariable, but tryparsamide acts less satisfactorily after previous administration of atoxyl (or other arsenicals). In advanced cases it is less certain, but in the absence of other debilitating diseases, and when degeneration of the central nervous system has not progressed too far, and when the cerebro-spinal fluid does not contain too many cells, tryparsamide gives gratifying results.

Optic neuritis.—Some are particularly sensitive to tryparsamide and optic neuritis is apt to develop in patients previously treated with smaller quantities, and to whom a second course is given. Sometimes it occurs after comparatively small doses and the Editor has seen three where blindness ensued in doses ranging from 5–13 grm. Jamot reported that, out of 25,638, 233 developed ocular troubles; in 30 amblyopia and in 17 amaurosis, but Basten, in cerebral syphilis, in a larger series, has not experienced the same amount of ocular trouble.

Ridley (1946) classifies disturbances of vision into four stages :-

(1) Metamorphopsia and a sensation of shimmering movement (objective).

(2) Depression of vision, loss of peripheral field for even large objects, followed by decrease in central acuity. The appearance of the optic discs still remains normal.

(3) After an interval of two weeks, pallor, unaccompanied by swelling and vascular abnormalities, appears in the optic discs and the victim becomes com-

pletely blind with very inactive \(\frac{2}{4} \) dilated pupils.

(4) Stage of recovery, which may proceed for three to six months, in which there may be complete return of central acuity with some degree of improvement in the peripheral fields. The pallor of the discs remains unchanged and may even progress. The central vessels, especially the arteries, become constricted and whitish, perivascular cuffs make their appearance around the larger vessels near the optic discs. Premonitory symptoms are photophobia, lacrymation, ocular pain and dimness of vision. It should, therefore, be made the rule to test the vision of each patient before injection by detection of some small object.

In any suspicious case administration of arsenicals should be suspended, remembering that the toxic action is often delayed and that optic neuritis may progress even after cessation of treatment. This was the case in the days when

atoxyl was employed.

OTHER ARSENICALS

Ethanarsol (monosodium salt of 2 p-arsono-arsilino-ethanol) and Propanarsonal (monosodium salt of 3 p-arsono-anilino-proponol) contain 20 per cent. of arsenic. When injected in doses of 2 grm. the action is comparable to that of tryparsamide, but they would appear to produce optical disturbances even more readily.

Neocryl (sodium succinanilo methylamide-p-arsonate) compares favourably with tryparsamide, is less toxic and possesses a similar comparable trypanocidal activity. Doses are similar, but the ultimate results in the second stage are

said to be less favourable.

N. phenyl glycineamide-p-arsonic acid, of which tryparsamide is the sodium salt, may be given by the mouth, which is, of course, simpler. In contrast to tryparsamide it is well tolerated by this route and causes disappearance of the trypanosomes from blood and cerebro-spinal fluid. By the parenteral route the dose is double that of tryparsamide, and is less apt to produce optic neuritis.

Mapharsen (mapharside) meta-amino-para-hydroxyphenyl-arsine oxide—is believed to be the compound elaborated in the body after injection of arsphenamine. The initial dose is 40 mgm. per kg. for women; 60 mgm. for men. It is as

efficient as neoarsphenamine, but 11 times as toxic. The sterilizing dose is $\mathbf{1}_{\mathbf{1}}^{\mathbf{1}}$ and the chemo-therapeutic index is double, whilst the curative index is slightly higher than that of neoarsphenamine.

Phenylarsenoxide— $\gamma(p$ -arsenophyl)-butyric acid—cures early cases, but is less

effective in later stages (Eagle).

Melarsen-oxide (p-arsenoso-phenylbutyric acid), Friedheim, a trivalent product, is very active on trypanosomes resistant to tryparsamide. Non-toxic in ordinary therapeutic dose of 10 or even 40 mgm. per kg., daily injections are well borne and apparent cures produced by 14–15 injections. It can be given by the mouth in doses of 150 mgm. for an adult, or by intravenous injections of 25 mgm. daily. McLetchie in Nigeria considers that it is too toxic in advanced cases. It is undoubtedly effective in a high proportion of intermediate and advanced cases. The results are similar to those of tryparsamide, but it is too toxic (Duggan and Hutchinson).

Melarsen (melaminyl-substituted phenylarsonate-4289)—the d-sodium salt was prepared by Friedheim and was tried out in West Africa. It was produced by him in combination with B.A.L. (or 2'-3'-dimercaptopropanol or dimercaprol) which renders it less poisonous and the compound is then known as melarsen B, mel B, or arsobal. It sterilizes the blood and causes improvement in the cerebro-spinal fluid. Duggan and Hutchinson (1951) found mel B in short courses of 8 injections at five-day intervals at least as effective as tryparsamide.

but toxicity is greater.

Melarsen B (Friedheim) is now known in France and Portugal as arsobal in 3-6 per cent. solution and as such it has achieved a reputation in the treatment of trypanosomiasis in Portuguese and French West Africa. It is claimed that early cases are cured by one dose of 4 mgm. per kg.; second stage cases with up to 20 cells in the C.S.F. by three doses in weekly injections. Late cases are treated with three or four courses of the above regime. Butursen (70A), an American product, is effective in early cases. The antimonial analogues—Msb and Msb₃—also produced by Friedheim, are said to be very active (Le Rouzic, 1949).

Azo-arsenobenzol (4197) traverses animal membranes. It was tried out by Friedheim in West Africa in doses of 0.5 grm. intravenously every few days and rapidly sterilizes the blood and lymphatic glands. In cerebral trypanosomiasis an initial dose of 0.1 grm. was found necessary in order to avoid Herxheimer reactions.

OTHER PREPARATIONS

Tartar emetic (sodium antimonyl tartrate), which was formerly much used, is curative for some forms of bovine trypanosomiasis, but it is now mainly directed to reinforce tryparsamide treatment in cases complicated by schistosomiasis.

Styrylquinoline compounds. Browning introduced aniloquinoline and styrylquinoline which protect mice against T. brucei. They have not been much used

in human trypanosomiasis.

Synthalin and undecane diamine.—These guanidine compounds were proved by Yorke to exert a direct lethal action on trypanosomes in vitro and thus led to the introduction of:—

Diamidino stilbene (stilbamidine) (see also p. 822). This was found to be active in experimental trypanosomiasis and was tried out in Nigeria and Gambia by Harding and Bowesman. Intravenous injections are apt to be followed by temporary symptoms, but it may also be injected intramuscularly. It banishes the trypanosomes, but is unsuited for cases with protein content in the cerebrospinal fluid above 0.05 per cent. The treatment takes about half the time necessary for tryparsamide.

Pentamidine was tried out by Lawson and Gilbert (1943) in Uganda and Northern Rhodesia as well as by Saunders on the Gold Coast. It was given daily for 18 days intramuscularly in doses varying from 1-6 to 5-15 mgm. per kg. Those with cell counts in the cerebrospinal fluid less than 30 per cmm. are usually cured. By the intravenous route at least 2 mgm. per kg. should be given. Serious fall in blood pressure is avoided by injecting the drug very slowly. A successful cure in a European was reported by Bomford (1944) with a total of 4·3 grm. in 39 days, in doses from 100–300 mgm. mostly on successive days, but McComas and Martin (1944) recorded a fatality in an African after three injections, death being due to a Herxheimer reaction. Polyneuritis has also been recorded. McLetchie in Nigeria considers that it is equal to antrypol. Pentamidine isethionate (lomidine) is the salt used: 100 mg. on the first day, then 200 mg. daily to the seventh day. Synergic action with tryparsamide, 6–9 grm., in seven days is beneficial in intermediate cases (Duggan and Hutchinson).

Propamidine possesses the same qualities, but is more toxic, causing abortion in pregnant women. The neuropathies which may follow prolonged administra-

tion of this group of drugs limit their usefulness (see p. 161).

Synergic or combined treatment.—Striking recoveries have been secured by combining antrypol and tryparsamide therapy—which is borne out by the experimental work of Yorke indicating that pathogenic trypanosomes may become drug-fast, and that resistance to antrypol is brought about very slowly. The Editor has recorded 11 European cases in which success was obtained by antrypol in tryparsamide-resistant cases and vice versa. The conclusions that may be drawn are that, when once clinical and parasitological relapse has taken place after an initial course of treatment with one trypanocidal drug, a change should be made to one of an entirely different chemical constitution. Thus preliminary antrypol treatment, in maximal tolerated doses, should be followed by tryparsamide in moderate doses—2 grm. twice weekly (or 4 grm. per week). Chesterman advocated two or three large doses of antrypol (three doses 1.5 grm. for an adult at three or four-day intervals) followed by 4-6 weekly injections of medium doses of tryparsamide—70 mgm. per kg. in children, 55 mgm. for adolescents and 45 mgm. for adults. Between the courses a rest of 10-14 days should be permitted until the urine becomes free from albumin before the administration of tryparsamide—alternating injections of tryparsamide and antrypol with intervals of three days have been given by Maclean in Nyasaland and have been advocated as the standard treatment by the Foréami organization in the Belgian Congo, and by McLetchie in Nigeria.

Sicé and Torresi found the best combinations were:—Antrypol and tryparsa-

mide, antrypol and anthiomaline, tartar emetic and treponyl.

Harding (1946) in Sierra Leone has compared the following types of treatment:

(1) Antrypol—5 doses of 1 grm. at 5-day intervals in cases with normal cerebrospinal fluid.

(2) Tryparsamide, 6-10 doses of 2 gm. at 5-day intervals (9-10 doses).

- (3) Antrypol—3 doses of 1 grm., followed by tryparsamide, 3–5 doses of 2 grm.—all at five-day intervals.
- (4) Two combinations of antrypol and tryparsamide, 3-7 doses of 2 grm. at five-day intervals:—
- (a) Antrypol—3 doses of 1 grm. followed by tryparsamide, 3–7 doses of 2 grm. An interval of five or seven weeks separated the first and second courses; the remainder were given at five-day intervals.

(b) Antrypol—2 doses of 1 grm., followed by tryparsamide, 4-6 doses of 2 grm.

at five-day intervals.

The cerebro-spinal picture was taken as the only reliable index of cure. In

mass treatment in Nigeria the total antrypol is 3.2 grm. followed by tryparsamide 10 grm. in 9 injections at intervals of 5 days. The first injection of 0.2 grm.

antrypol is a test for idiosyncrasy.

General considerations.—The mode of action of trypanocidal substances has been explained in the introduction by Yorke and his colleagues in 1930 of culture media in which pathogenic trypanosomes can be kept alive and active in undiminished numbers for at least 24 hours at 37° C., thus enabling observation to be made in vitro in a medium comparable to the body fluids in animals and man. Another valuable method was the use of the fluorescent microscope. The substances absorbed by the trypanosomes can be seen as fluorescent particles with ultra-violet rays. By such means qualitative estimation of drug concentrations in the blood can be made. Thus the pentavalent compounds of arsenic and antimony have only a slight trypanocidal action in vitro, whilst the trivalent compounds are much less active. It was concluded that the therapeutic action of the trivalent compounds was entirely due to a trypanocidal power and that the pentavalent compounds became active only after reduction in the body to the trivalent form. It was found also that resistance of trypanosomes to aromatic compounds of arsenic and antimony did not consist of resistance to metals, but to the various substituted phenyl radicals and was not dependent on the host.

Acquired resistance is due to the fact that the drug was no longer absorbed by the trypanosomes. Resistance was produced by drugs in vitro and was easily brought about by aromatic arsenicals and antimonials. Natural drug resistance of T. gambiense to tryparsamide is commoner than generally believed and it appears that a trypanosome can suddenly acquire a certain degree of arsenic

resistance by passage through unaccustomed hosts.

Transmission of drug-resistance through the tsetse.—Yorke and his colleagues discovered an important fact—that strains of trypanosomes possessing a high degree of resistance are transmissable by the tsetse (transmission of an acquired character) and that this remains unimpaired after two successive passages through the fly; but Van Hoof on the Congo has found that the non-resistant strains are usually more easily transmitted. Resistant strains which can be transmitted with great difficulty are derived from chronic well-treated cases. These more resistant strains usually constitute the minority.

Prophylaxis.—Prophylactic measures are based principally on the habits of Glossina palpalis, G. tachinoides and other species which may transmit T gambiense. The measures employed are so similar to those in use against T. rhodesiense and so interwoven that they must be considered together in the section on the bionomics of glossina (see p. 1051). Other control measures consist of fly traps, barriers, clearings, block systems and the employment of DDT to destroy adult flies (see p. 865). Complete scientific prophylaxis can be established with certainty only after we are in possession of full knowledge of the habits of the tsetse and the reasons for their restriction to limited and capriciously distributed areas and also of the vertebrate hosts of the trypanosomes.

Destruction of big game.—The abolition of big game has been undertaken in N. and S. Rhodesia and in Tanganyika on an extensive scale. Unfortunately it appears to be true that where antelopes and buffaloes exist in large numbers there the tse-tse is to be found in abundance. In areas which have been cleared of these animals the destruction of the tse-tse appears to be a practicable proposition. An experiment in this direction was undertaken in a large block, comprising 700 sq. miles, in the vicinity of Shinyanga, Tanganyika. Originally large numbers of G. morsitans, G. swynnertoni and G. pallitipes were present. Measures commenced in July, 1945, and since that date 8,500 head of animals have been destroyed. The larger big game have been eliminated and a great reduction of

impala and reed buck has taken place. As a result G. swsynnertoni has now disappeared and a great reduction of G. pallidipes has been recorded.

Repellents.—Little information is obtainable on this subject, but Holden and Findlay (1944) found that an anti-mosquito cream (containing pyrethrum) has a repellent action chiefly against *G. palpalis* for six hours, when applied to the skin, but this action is apt to be destroyed by heavy sweating with exposure to strong sunlight. The most popular at present is *Dimeepol* which contains dimethyl phthalate and ethylhexandiol in non-greasy basis and can be dissolved in a small amount of liquid paraffin for use in fly country.

Chemoprophylaxis.—A prophylactic injection of antrypol does not prevent actual infection, though it does mitigate the pathogenicity of the infecting trypanosomes. Fourché, on the Congo, concluded that intravenous injection of 1 grm. in adults, and 0·3 to 0·75 grm. in adolescents is of definite prophylactic value for seven months, but McLetchie in Nigeria has reduced this figure to six weeks. Van den Branden injected all the inhabitants of a village in the Belgian Congo with the following doses: adults 1 grm., adolescents 0·5 grm. and children 0·25 grm., infants 0·18 grm—each receiving two injections. Duke's statistics in Uganda seemed to indicate that prophylactic action may last three weeks. Olovitch (1927) reported favourably on mass injection (or moranylisation) of the native population of the Belgian Congo.

In Sierra Leone Harding and Hutchinson (1950) think that in that country a stage has been reached when it is justifiable to undertake mass prophylaxis with pentamidine. A trial of pentamidine in French West Africa was successful in protecting over 1,000 persons for six months whereas 19 infected cases were found in 902 controls (Brun-Buisson).

Propamidine has the same action as pentamidine. An experiment in drug prophylaxis with propamidine was carried out in the Belgian Congo and has been described by Fain and de Mulder (1949) who have demonstrated that two intramuscular injections of 300 mgm. for men (less for women and children) at an interval of six months served to protect for a period of two years, though examination of the cerebrospinal fluid showed that a cryptic infection still persisted. Controls, however, showed many more infections. They assert that even a single dose has considerable protective value.

The latest results of Van Hoof and his colleagues in the Congo are as follows: they find that one dose of pentamidine (30 mgm. per kg. body weight) injected intramuscularly can protect for six months. This appeared to be optimistic. The average weight of the Congo native is 40 kg. and, by raising the injection to 5 mgm. per kg. for protective action, good results have been obtained. It should be noted that the isethionate salt is used; not the hydrochloride. Both propamidine and pentamidine isethionate should be given in 1.25 per cent. solution intramuscularly. McLetchie in Nigeria considers 100 mg. pentamidine isethionate intravenously constitutes the best and most enduring method of protection.

Other prophylactic measures.—Brilliant results have attended the efforts of the Portuguese to combat sleeping-sickness in the island of Principé. where the annual mortality from the disease amounted to 83 per thousand of the population, and the local industry (cocoa) was threatened with extinction. Besides jungle-clearing, drainage, blood examinations, segregation of the infected, and destruction of possible animal reservoirs of the trypanosome, natives, dressed in white and carrying on their backs a dark cloth smeared with birdlime, were sent into the jungle, and every night the flies caught were removed and counted. In three years 470,000 glossinæ were caught. As a consequence of this combination of sanitary measures the fly and the sleeping-sickness were exterminated.

Of course, it was only the complete isolation and the limited size of the island that made such a result possible.

The Anchau experiment in Nigeria has provided a model example of the method of clearing an area of tsetse flies as well as of benefiting the population generally and of raising their level of culture. Anchau is now a tsetse-free corridor, linking two of the railway lines that diverge from Zaria, and is some 65 miles long, over 600 square miles in extent and with a population of 50,000. The combination of partial and barrier clearings has proved effective. The work on this scheme entailed preparation of maps, surveys, construction of roads, clearing 110 miles of stream, sinking of wells, study of local soils and vegetation, agricultural experiments and monthly fly surveys. The land allowance is 4-3 acres per person. Areas are reserved for plantation of wood and grazing.

Removal of infected populations.—Trypanosomiasis has interfered with the development of one-quarter of the African continent. In Uganda by 1900 it was estimated to have exterminated two-thirds of the native population. To preserve the hitherto uninfected from trypanosome infection, the Government transported the entire population of the Sesse Islands and neighbouring shore of Victoria Nyanza to fly-free areas in the interior. It was hoped that, the human source of trypanosome supply being thus denied them, the tsetse flies would cease to be infective. Unfortunately, this hope has been disappointed. Three years after the depopulation of the districts involved, Bruce ascertained that local flies could still convey the disease to laboratory animals. Manifestly, T. gambiense can flourish under natural conditions in vertebrates other than man. The reservoir host in this instance was found to be the situtunga antelope.

Dispersal of tsetse flies by traffic.—The opening up of Central Africa by motor roads and the development of motor traffic has introduced a new problem in the spread of trypanosomiasis, both gambiense and rhodesiense infections. Jack has shown the tendency of these flies to follow up moving objects and to settle on the backs of pedestrians and cyclists and under the hoods of motor cars. On pedestrians these flies may be carried 10, on motor cars, 50 miles a day. When the moving object stops, the flies move away and seek shade nearby. It has been found necessary to restrict vehicles (including cycles), leaving fly areas, to fixed routes. At the point of exit notices are placed stating that motorists and cyclists must submit to prescribed measures. Native cyclists are cleansed of flies in special gauze cages. Motors are fumigated with "Flit" and the passengers are groomed with insect-nets.

Prognosis—The state of the C.S.F. is most important. Increase of total protein is of more significance than cell increases. If the C.S.F. is abnormal after treatment the cell count is the more delicate indicating cure or failure. The Sicard Canteloube method of estimating total protein (normal 22 mg. per cent.) should be used. The blood sedimentation rate is also useful.

[For a detailed description of tsetse flies (Plates IV, V) and preventive measures at present in use, see pp. 1055-1057.]

RHODESIENSE SLEEPING-SICKNESS

The trypanosome found in cases of human sleeping-sickness originating in Rhodesia was at first considered to have certain peculiarities when inoculated into the rat. This fact, together with the greater virulence of the disease both in man and in laboratory animals, and the greater resistance to arsenical treatment, led Stephens and Fantham to separate it as a distinct species under the name of T. rhodesiense, in 1910. Later, it was proved that it is transmitted by Glossina morsitans (Kinghorn and Yorke), not by G. palpalis, and that G. swynnertoni is also an efficient intermediary.

Kleine regarded T. rhodesiense as the form taken by T. gambiense when introduced into a new area and transmitted by tsetse flies of the morsitans group, and as distinct from T. brucei; whereas Duke considered T. rhodesiense and T. brucei the same; whilst Lavier held that T. gambiense, T. rhodesiense and T. brucei are one and the same species. On the other hand the International Commission on Human Trypanosomiasis concluded that T. rhodesiense is merely T. gambiense transmitted by a different species of tsetse, viz. G. morsitans.

Yorke and his collaborators pointed out that the selective cytolytic action of normal serum on trypanosomes and the resistance of T. gambiense, in contradistinction to T. rhodesiense, may be the true explanation. By this test, T. rhodesiense and T. brucei appear to be identical, but the serum resistance of T. rhodesiense is not a fixed or stable character, but one which is readily acquired and quickly lost. The fact is that there are no constant differential characters in these two human trypanosomes. The rhodesiense type is undoubtedly more virulent than gambiense, as the latter has become habituated to man by long residence in his body, whilst the former is a more recent acquisition associated with G. morsitans, and usually with big game, especially antelopes.

The modern biological view is that the trypanosomes are members of an intraspecific unit, and that they have originated from *T. brucei*, probably from some antelope strain.

Geographical distribution.—Rhodesian trypanosomiasis occurs in North-Eastern Rhodesia, especially in the Luangwa Valley, about the southernmost limit, 14° S.; throughout Tanganyika Territory; in Portuguese East Africa; in Nyasaland, especially in the region south and west of Lake Nyasa: in fact, its distribution closely corresponds with that of G. morsitans in East Africa. (Map I.) A virulent outbreak at Mwanza, Tanganyika, was transmitted by G. swynnertoni.

Ætiology.—In human blood (Fig. 18-1, 2), T. rhodesiense is morphologically indistinguishable from T. gambiense and T. brucei: but if it is passed through the rat or guinea-pig, a small but variable proportion of the parasites, especially the stumpy forms, will be seen to have their nuclei located posteriorly to the kinetoplast—that is to say, at the non-flagellar end of the organism (Fig. 18-3, 4, 5, 6). This feature, formerly considered specific, is not now regarded as important, because similar changes are undergone by other trypanosomes.

A good deal of work has been expended in attempting to prove and disprove that T. rhodesiense is no other than a strain of T. brucei inoculated into man. When injected into rats, T. brucei exhibits the same proportion of posterior-nucleated forms as T. rhodesiense (Bruce). Taute and his fellow-workers disproved this conclusively by inoculating themselves and 129 native porters with dog's and mule's blood containing T. brucei, with a negative result, while rats, dogs and a goat, inoculated with the same blood at the same time

succumbed. In 1936 Sicé proved polymorphism and posterior-nucleated forms existed in T. gambiense.

Pathology.—The visceral lesions of T. rhodesiense trypanosomiasis are probably more often fatal than lesions of the central nervous system. Hawking and Greenfield (1941) described extensive trypanosomal effusions in pleural, peritoneal and pericardial cavities, associated in the latter

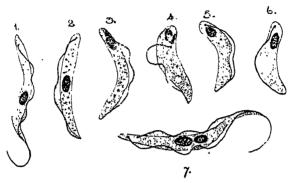


Fig. 18.—Forms of Trypanosoma rhodesiense. (After Laveran.)
1, 2, Normal forms in blood of man; 3-6, various stages of posterior displacement of the nucleus; 7, a dividing form.

instance with inflammation of myo-, epi- and endocardium. The cerebrospinal fluid contained numerous trypanosomes, but the lesions in the nervous tissue were singularly slight, being limited to a histiocytic infiltration of the cerebral membranes. The cell count and protein content were not much raised.

Symptoms are similar to those evoked by T. gambiense, though febrile paroxysms are more frequent, and severe glandular enlargement is not often met. The disease generally runs a much more rapid course, and fatal symptoms usually supervene within a year of infection, death taking place from convulsions. Acute mental symptoms, such as mania, are frequent.

Buchanan observed that rapid emaciation, weakness, fever and cedema constitute the most obvious signs of toxic action resulting from this infection, while careful observation on the heart showed that in nearly every one there is a marked effect on the cardio-vascular system, with irritability and tachycardia. The characteristic erythematous rash is usually marked.

The course of the infection is usually so rapid that patients succumb before the sleeping-sickness stage develops.

Lamborn and Howat (1935) recorded that very mild and almost symptomless infections may occur in natives of Nyasaland. The parasites are quite numerous in the bloodstream, but are not seen in the glands or cerebro-spinal fluid. On inoculation into animals a virulent infection ensues. Similar cases were reported by Woolf in the valley of the Rovuma River in Tanganyika in 1910, and it has been shown that these symptomless carriers may be the starting point of an outbreak.

Diagnosis is the same as for T. gambiense. In acute cases trypanosomes are plentiful in the peripheral blood and diagnosis can readily be made by examinations of thick drop specimens. Possibly the parasites are more easily demonstrated by lymphatic-gland puncture. Thus, Kleine found, in a series of 32 cases, 24 had trypanosomes in their glands and blood; 4 in the glands, but not in the blood; and 4 in the blood only.

Corson proved, in a self-inflicted experiment, that a local circular erythema with a darker and slightly tender centre is a useful indication

of an infective bite by glossina in light-skinned people.

TREATMENT

Tryparsamide and other preparations (see pp. 126–127), which are of use in T. gambiense infections, appear to be relatively powerless in T. rhodesiense cases, but tryparsamide has been used along with antrypol (suramin) with success (see Maclean, p. 129). Unfortunately, some of the apparently cured cases which were then recorded have subsequently relapsed. Recent reports indicate that melarsen B, or arsobal, is the most active drug in this trypanosomiasis. Goodwin (1953) has suggested that pentamidine is specially effective as shown by Keevill and de A. Silva in Mozambique who has reported success in 22 out of 25 acute rhodesiense infections. The trypanosomes decreased in numbers within 16 hours and disappeared in 28.

In resistant cases the substitution of pentamidine isethionate and tryparsamide proved more effective, but there are areas where the antrypol-pentamidine

combination gives the greatest number of successes.

The treatment with antrypol (germanin) is more hopeful, and remarkable successes have so far been recorded; in fact the drug appears to exert a much more immediate action than in T. gambiense infections. Dye, in Tanganyika Territory, advised intravenous injections on the first, third and fifth days, and subsequently at intervals of five to seven days till a total of 7 grm. has been administered, and claimed the disappearance of the trypanosomes from the peripheral blood took place within twenty-four hours. Antrypol, no doubt, has a remarkable sterilizing effect in early hæmic infections.

Prophylaxis.—Prompted by his investigations of the hypothesis that big game act as a reservoir for *T. rhodesiense*, Yorke advocated the extermination of this fauna, but recent investigations tend to show that these conclusions were premature and that man himsel may often be the chief source of infection. Jack, in Southern Rhodesia, studying the behaviour of *G. morsitans*, found that the fly was attracted to man by stimuli of movement or scent. Dark colours were most attractive, especially black. White clothing appeared to have some protective value.

Other prophylactic measures are the same as those advocated for *T. gambiense*. (See p. 130.)

Prophylactic injection of antrypol.—Duke (1934) showed by experiments on human volunteers that the prophylactic action of antrypol is more effective against *T. rhodesiense* than *T. gambiense*. (See p. 131.)

For further details of African trypanosomes, see Appendix, pp. 905-907.

II. SOUTH AMERICAN HUMAN TRYPANOSOMIASIS

Synonym. Chagas' Disease.

Definition.—Usually an acute, more rarely a chronic disease, caused by *Trypanosoma* (Schizotrypanum) cruzi, and disseminated by certain reduviid bugs. The acute stage of the disease is characterized by diarrhea



MAP II South America, showing distribution of S. American trypanosomiasis (Chagas' disease)

and enlargement of lymphatic glands and spleen, accompanied by cerebral symptoms. The chronic form may manifest special symptoms, according as the heart or other important organs are most invaded by the parasite.

Geographical distribution.—In the provinces of Minas Geraes, São Paulo, Rio Grande do Sul, and Goyaz in Brazil; in the states of Trujillo and Miranda in Venezuela; and in the Western Argentine in Tucuman and Jujuy; in children in Cordoba, Argentina, and in the Catamarca province. (Map II.) The disease has also recently been found in Panama and in Guatemala, in Bolivia, Peru, Ecuador, Chile (provinces of Tarapacti and Jurico), in Venezuela, San Salvador, in Uruguay, Colombia, and in Mexico.

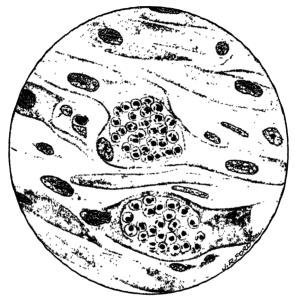


Fig. 19.—Trypanosoma cruzi: schizogony in heart-muscle. (From a preparation by J. Gordon Thomas.)

Trypanosoma cruzi, or trypanosomes resembling it, have been found in bugs (Panstrongylus, Triatoma and Rhodnius) in California and in Texas, but they apparently do not transmit the disease to man in these regions.

Ætiology.—During the febrile attacks the parasite, *T. cruzi*, can be found only sparingly in the blood, though in the acute disease, as seen in children, it is more abundant. In chronic cases, in which the clinical symptoms may be puzzling, parasites are apparently absent. Apparently in human beings this is a disease of childhood, but in Panama a case has been found by Ludeberg in a man of seventy-seven.

This trypanosome was at first referred to a separate genus, Schizotry-panum, on account of its distinctive method of multiplication in the human body. Instead of the longitudinal division which occurs in other species of trypanosomes, this parasite proliferates in the cells of the internal organs, especially in the interior of striated muscles, such as the heart. Two forms, one slender, the other broad, are found in the peripheral blood. In the internal organs multiplication takes place by schizogony

(Fig. 19) at a very rapid rate, the resulting forms resembling leishmania bodies which, four days later, become transformed once more into trypanosomes that invade the blood-stream. (For a complete account of the parasite, see Appendix, p. 908.) This trypanosome, as it occurs in the blood, can be distinguished from other human trypanosomes by its peculiar "C"-shape, and by the oval appearance of the kineto-nucleus. Dividing forms are never seen in the blood. It is by no means certain whether it is related to, or identical with, Trypanosoma vespertilionis in bats.

T. cruzi is easily cultured on N.N.N. medium, in which it assumes the

stunted forms usually seen when it is found in its definitive hosts.

The reservoir-hosts of T. cruzi are animals peculiar to the country in which the disease occurs; there are various species of armadillo, opossum and others (see Appendix, p. 911).

It is possible that closely related trypanosomes—T. rangeli and T. ariartii—may also be responsible for a certain number of cases (Fig. 231) (see p. 912).

Transmission.—The adult trypanosomes are ingested by the intermediary invertebrate host, the bug, Panstrongylus megistus, either in its larval, nymphal, or adult stage (Fig. 399, p. 1067). After they have passed through many stages in the intestinal canal, in a period of 8-10 days, fully formed trypanosomes, known as "metacyclic" forms, re-appear in the hindgut and are passed out through the faces of the insect. Infection of man, therefore, probably takes place when the insect defecates into the wound caused by its bite. The original idea of C. Chagas (1909) that infection is conveyed by the bite of the panstrongylus has not been confirmed. Mayer stated that infection may be conveyed through the bug in a hereditary manner. In the Northern Argentine the common host appears to be the "Unchuca" (Triatoma infestans); in Uruguay T. rubrivaria, but many other species of the genera Panstrongylus, Rhodnius, Eraturus and Triatoma can transmit the infection. Fifteen species of Triatomide belonging to four genera can transmit infection in Brazil, but only three are of epidemiological importance-P. megistus, T. infestans and T. sordida (see Appendix, p. 1067).

Under experimental conditions, all laboratory animals can be readily infected, and under natural conditions the domestic cat has been found to harbour this trypanosome. Developmental forms have been found in bugs as far north as Utah. In infected animals transmission from the parent to the offpsring in utero can apparently take place, according to C. Chagas, who originally affirmed that congenital transmission frequently takes place in man. The marsupial opossum of Australia (Trichosurus vulpecula) is susceptible (Backhouse).

Pathology.—The post-mortem appearances have been described in children. The heart is usually enlarged and there is an excess of yellow or greenish pericardial fluid, sometimes containing a few fibrinous flakes. In microscopic sections there is evidence of diffuse myocarditis and between the muscle fibres there is extensive infiltration of lymphocytes, plasmocytes, macrophages and round cells. There is enlargement of the spleen, parenchymatous degeneration of the liver, and general enlargement of the mesenteric glands. The thyroid gland, as a general rule, is congested and hypertrophied. There is general infiltration of the subcutaneous tissues and thickening of the serous membranes. Subserous ecchymoses are

common, and small hæmorrhages in the brain and spinal cord have been described. The skeletal muscles appear to be the seat of election for multiplication of the parasite, and the changes are essentially similar to those in the heart. The gross lesions in the various organs are due to the presence of the parasite. Under the microscope, cyst-like cells, containing leishmania forms, can be found, particularly in the striated muscular fibres, and in those of the heart. When the suprarenal glands are affected,

pigmentation of the skin and other evidence of Addison's disease have been observed. The blood does not show great changes, as a rule, but in the acute stages considerable leucocytosis with mononuclear increase has been recorded. The trypanosome may persist without causing severe anamia for a very long period, and has been found in the blood of a man twenty-five years of age who exhibited no marked symptoms of disease.

Symptoms.—Attention has been drawn to a primary lesion—termed by South American observers a chagoma—which results from invasion of the skin and surrounding tissues by proliferating trypanosomes. This takes the form of a local inflammatory swelling, in which leishmanial forms of the parasite multiply within the fat cells. This is followed by a centripetal



Fig. 20.—Unilateral conjunctivitis as an early sign of infection with T. cruzi. (Publication No. 24, Universidad Buenos Aires.)

lymphangitis with formation of nodules along the path of the vessels. Mazza and Freire described similar lesions which they considered hæmatogenous as well as cutaneous swellings, the size of olives, adherent to the skin, in the suprahyoid, pectoral, and other regions. On the chest they may be as long as 8 cm., raised above the level of the skin, of cartilaginous consistency and violet-red. Some fourteen days after the infecting bite a rash may be seen (Mazza and Mizara) on chest and abdomen, consisting of sharply defined red spots, the size of a pin's head. There is no pain or itching, and the exanthem fades entirely within seven to ten days. Some three weeks from the time of infection ædema of the eyelids, sometimes also of the malar and temporal regions, together with unilateral conjunctivitis (Romaña's sign) is noted (Fig. 20). There are some reasons for believing that occasionally the conjunctiva may be the port of entry for T. cruzi, as E. Chagas has shown experimentally (by placing the excreta of bugs on the rabbit conjunctiva). Furthermore, in an accidental laboratory infection recorded by Herr and Brumpt, the site of entry was undoubtedly the conjunctiva, and infection was followed by dacrocystitis, swelling of the face, pyrexia and adenitis. According to Talice and Rial dacrocystitis may be uni- or bilateral and is invariably accompanied by facial cedema.

Enlarged lymphatic glands containing leishmania forms of T, cruii are described by Mazza, in association with the inoculation chagoma, in satellite lymphatic dissemination, as well as generalized lymphadonitis.

The further course of the disease is at present rather obscure. Chagas (1934), in an experimental inoculation of a patient suffering from incurable malignant disease, observed no outstanding manifestations beyond intermittent pyrexia. Trypanosomes appeared in the blood on the

thirty-eighth day.

There have been so many discrepancies in the published accounts of the clinical manifestations that it is difficult to describe any particular symptoms as distinctive. Some believe that there are none. Miller, for instance, found his Panama cases distinctly negative, and the trypanosomes vanished from the peripheral blood within the course of a few weeks. Reichenow (1984), working in Guatemala, observed several symptomless cases and thought that the infection may differ in intensity in different countries. There, about 3 per cent. of children of five months of age were infected, and trypanosomes were present in the bloodstream for ten to thirty days.

Chagas and his colleagues described an acute form with pyrexia, especially in infants, with general anasarea and thyroid enlargement, and sometimes also with general lymphadenitis. The liver and spleen may both be enlarged. In the terminal stages the child develops symptoms of meningo-encephalitis. Mazza and his colleagues describe an intermittent quotidian type of fever with a double peak as strong presumptive evidence of Chagas's disease. Intermittent fever persists as long as the trypanosome is present in the blood. The chronic form, according to Brumpt, may assume a myxedematous, cardiac or nervous complexion. The former is frequent in children up to fifteen years of age and is characterized by thyroid insufficiency, scanty urine and dry skin. The cardiac type is characterized by cardiac arrhythmia and extrasystoles with brachycardia; the nervous type by intention tremor and various paralyses.

Kraus has pointed out that it is difficult to distinguish endemic goitre and cretinism, which are frequent in the geographical range of this disease, from acute and chronic trypanosomiasis as depicted by Chagas. Munk has found that in Brazil, where Chagas made his observations, 75 per cent. of the population normally has goitre and there is a cretin in almost every family. It is therefore more than likely that the signs of thyroid insufficiently formally ascribed to

Chagas' disease are not, in fact, due to it.

An account by Talice and Rial (1941) described an investigation of 165 acute infections in children in Uruguay. The diagnosis was established by the xeno-diagnostic method. There were two deaths from myocarditis, established at autopsy. More extended practice with the viscerotome (p. 849) has established the fact that death in Chagas' disease is usually due to involvement of the myocardium. Meningo-encephalitis has been described as an early or later manifestation.

Diagnosis.—The trypanosome is usually present in very small numbers in the bloodstream, and prolonged search may be required. It may be necessary to collect the blood in citrated saline and subject it to lengthy centrifuging. The parasites may sometimes be found in the cerebrospinal fluid by lumbar puncture, but puncture of the lymphatic glands or of spleen, bone marrow occasionally reveals them. A readier method of

diagnosis is to inoculate a guinea-pig with the patient's blood; the developmental stages of the parasite may be found subsequently in the organs. In the acute form positive results are said to be obtained in 26 per cent. of cases, but in chronic cases animal inoculation is negative.

These difficulties in diagnosis have led to the elaboration of a complement-fixation test (Machado, Villela and Bicalho). The antigen is prepared from a glycerin extract of heart and spleen of infected animals. Lacoste, using a glycerin spleen extract of infected puppy, recorded positive reactions in 68.5 per cent. (Machado). Recently, however, artificial cultures of *T. cruzi* have provided a more reliable antigen. The specificity of the test against other forms of human trypanosomiasis must be accepted with reserve, but it seems evident that there is no parallelism between the Machado and the Wassermann reactions. An intradermal test was introduced by Mayer and Pifano, using an extract, "Cruzin," prepared from cultures of *T. cruzi*.

Brumpt suggested a method of xeno-diagnosis which consists in feeding laboratory-bred *Panstrongylus* with the blood of the suspected person, and demonstrating the cyclical development of the trypanosome in the intestinal tract. Borzone's modification of Brumpt's method consists of collecting 10 ml. of blood in a dry syringe. It is then placed in a watch glass and 4–6 larvæ of *T. infestans* are fed on it under cover in a bell-jar which is kept in darkness. When engorged they are set apart at 37° C. and their fæces are examined from time to time during two months.

Differential diagnosis.—On clinical grounds, Chagas' disease is to be distinguished from endemic goitre, ancylostomiasis, Graves's disease, cretinism, myxœdema, Addison's disease, and other disturbances of the endocrine glands.

Treatment.—Spontaneous recovery in febrile cases has been recorded.

Treatment has been carried out in Brazil by Mazza and his colleagues with Bayer 7602 (Ac) and since 1940 with Bayer 9736 (As). The former is a quinoline derivative; the latter contains 22 per cent. of arsenic and 5 per cent. of sulphur. The dose of 7602 is 22.2 mgm. per kilo; 5 ml. of a 8 per cent. solution is given intramuscularly, rising gradually to 20 ml. According to Talice and Rial, this compound acts directly on the trypanosomes and indirectly reduces the leishmanial forms in the tissues. Five injections are given on alternate days. 9736 is less toxic and better tolerated than 7602, and is given intravenously in 10 per cent. solution. The usual dose is 1.5 ml. (0.15 grm.) for adult men, and less for children and women, increasing to 3.0 ml. and even 4.5 ml. It is given twice or thrice weekly to a maximum total of 50 ml. (5 grm.) in men, 40 ml. for women, and 30 ml. for children. Certain phenanthridium salts (Browning and Leckie) also appear to be effective.

Prophylaxis.—This should be directed principally to the suppression of the insect concerned—Panstrongylus (Triatoma) megistus (Fig. 399, p. 1C67.) This is a large black insect belonging to the family Reduviidæ, well known to the natives, who call it "barbeiro," because, presumably, of its fondness for the face.¹ The nymphs bite and can convey the infection, but the adults, having wings, are more dangerous. In the daytime they live in the grass walls and roofs of the dirty native houses, or of pigsties, coming

¹ To Americans these insects are known as "kissing-bugs" because of the lesions they produce on the eyes and lips.

out after dark in search of their food—blood. Their habits indicate better and cleaner housing, sleeping off the ground, and protection by mosquito-netting. DDT and BHC have been used for destroying reduviids (Chapter LII). Pelloux speaks highly of SNP (Thiophosphate-o-diethylo'-paranitro phenyl) either in emulsion or dust. The former in 1 per cent. solution at the rate of 200 ml. per sq. m. kills triatomata.

The fact that the armadillo is the reservoir-host suggests that human habitations should be placed as far away from the burrows of these animals as possible, and that the floors of the houses should be constructed so that the armadillo cannot burrow underneath them. Brumpt has called attention to the fact that one form of reduviid, Panstrongylus geniculatus, which normally feeds on the armadillo, is commonly met with in the burrows of a Rock, or Moco, cavy, Kerodon rupestris, and that the trypanosome can be found in these bugs at great distances from any human habitation. Spontaneous infection of local armadilloes has been reported. It is, therefore, possible that the disease exists independently of man. Robertson has also found large numbers of this trypanosome in the blood of an opossum (Didelphis) in Honduras. (See also p. 911.)

CHAPTER VI

LEISHMANIASIS

UNDER the title "Leishmaniasis" at least three diseases are included—Kala-azar, Oriental Sore, and Espundia. (Map III.) These, though clinically quite distinct and having each a definite topical and geographical distribution, are all associated with what, optically, at any rate, appears to be the same organism, Leishmania.

I. KALA-AZAR (VISCERAL LEISHMANIASIS)

Synonyms. Tropical Splenomegaly; Black Sickness; Sirkari Disease; Sahib's Disease; Burdwan Fever; Dum-dum Fever; Ponos (Greece); Mard el Bicha (Malta).

Definition.—An infective disease characterized by chronicity, irregular fever, enlargement of the spleen and often of the liver, and the presence in these and other organs of *Leishmania donovani*.

Geographical distribution.—India—Assam, Madras—along Ganges and Brahmaputra. China—N. of Yangtse R. between coast and line joining Peking-Hankow; Provinces of Kiangsu, Shantung, Chih-li, north to Jehol, Fengtien, S. Manchuria and Mongolia. S. Canton. Sudan—Kassala and Blue Nile districts. Abyssinia—S.W. Omo river and N. of L. Rudolf. N. Kenya—Uaso Nyiro river and Nairobi-Addis Ababa road, Kitui reserve. Italian Somaliland near Cape Gardafui; Senegal, Dakar, Chad and French Niger Territory, Gambia (Gunjivo), N. Nigeria, French Guinea, Cameroons, Congo, Tunis, Tripoli, Morocco, Algeria, Egypt (rare), Sicily (Catania), Italy, Corsica, Crete (Canea), Spain (Marid E. and S. Coasts), Portugal, Turkey, Hungary, Yugoslavia, Cherbourg, S. France (Marseilles), Greece (Messinia and Peloponnese), Athens, Salamis, Macedonia—Salonica, Drama, Serres, Kavalla, Grecian Archipelago, Malta, Transjordania, S. Arabia (Yemen), Russia W. and E. of Caspian, Transcaucasia and Turkestan, Persia (Reid), Shiraz, Abadan.

S. America—N.E. Brazil, Sergipe—Araca-ju, N. Bolivia, N. Argentine, Chaco, Oran, Tabacal, Paraguay, Colombia, Venezuela—States of Guárico and Bolivar, Guatemala (Cabrera). (Kala-azar was first discovered in Paraguay by Migone in 1913.) The routine use of the viscerotome brought many fatal cases to light. At first the parasite was provisionally separated as L. chagasi, but it has been shown that there is no valid distinction from L. donovani. In its epidemiology it resembles the Mediterranean form, whilst naturally-infected dogs and cats have been found in endemic areas in Brazil.

Epidemiology.—The main information on epidemiology has been gained from the Assam epidemics which, beginning about 1870, have recurred at irregular intervals since. The epidemic advanced slowly along the Brahmaputra Valley at the rate of some hundred miles in seven years. Its introduction into a village has usually been traced to some individual from an infected locality.

Generally it clung to a place for six years and then disappeared without any apparent change in local conditions. A house seemed to retain the infection for many months, and natives considered it dangerous to re-occupy under a year. In 1922-3 it extended up to the headwaters of the river at Dibrugarh where it had never been known before.

At the present time kala-azar is confined to Assam, Bengal, Bihar and Orissa and the United Provinces as far as Lucknow. It stretches patchily down the

East Coast of India as far as Tuticorin.

On account of its deadliness, kala-azar, as it swept onwards, became a terror to the natives. Those suffering from the disease were turned out of the villages; sometimes they were made unconscious with drink, taken into the jungle and burnt to death. Some villages cut off all communication with neighbouring villages for fear of infection; other villagers deserted their homes and even migrated to a different district.

The neotropical form occurs in various types of country—in miserable hovels,

in dense forests, in desert country and on river banks.

It has been remarked by Kirk that the patchy distribution of kala-azar in the Sudan somewhat resembles that of Brazil. Here the disease is endemic in the Kassala and Fung districts bordering the Abyssinian and Eritrean frontiers. Hence the endemic area extends westwards as far as the White Nile. In the southern Sudan an endemic focus was found in the Kapoeta district, which lies between Abyssinia on the east and Kenya and Uganda on the south. A third endemic area exists in Darfur, the most westerly province of the Sudan.

Archibald and Henderson have shown that kala-azar is found in particularly restricted areas in eastern Sudan, especially along the Blue Nile and its tributaries from the Abyssinian border to within 150 miles south of Khartoum; there the river flows through open, flat plains of thick loam, where the temperature rarely

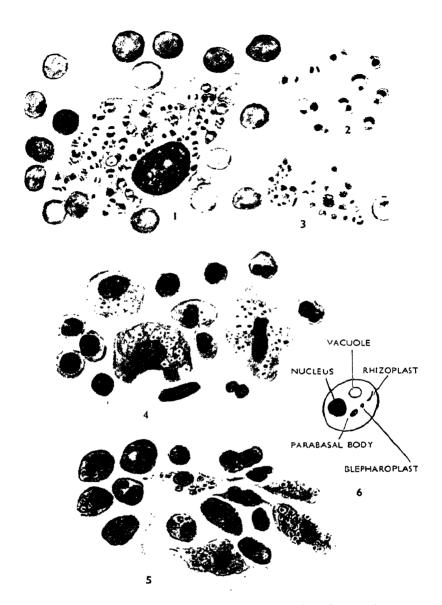
falls below 60° F.; the disease particularly attacks ill-fed children.

Giraud states that in the Marseilles district the disease has been apparent since 1922, 146 cases having been recorded. The endemic zone does not extend west of the Rhône in dry, scrubby districts where "fièvre boutonneuse" is most abundant.

The outstanding epidemiological features of the disease in India and China are that it is confined to rural districts, especially alluvial plains, and does not usually occur above 2,000 feet. The temperature conditions are a monthly mean maximum below 100° F. and a monthly mean minimum above 45° F. In India a high degree of humidity is a common factor: not so in China. In the Mediterranean the greatest number of cases occur from March to May; in Assam, in the cooler months from November to February; in the Sudan, after the rains between August and December; in China no seasonal incidence has been observed.

Napier states that an outbreak is usually determined by a concatenation of climatic and other factors such as widespread distress after an earthquake or an influenza epidemic which determine a general increase of cases. When all susceptibles, especially the children, have been attacked, all those in fact who were spared from the last epidemic, then and then only the disease dies down.

Mediterranean form.—In 1904, leishmaniasis was discovered in Tunis by Cathoire, and important studies by the Sergents, Nicolle, and many others showed that the parasite occurs in many of the islands and countries in the Mediterranean basin, especially Sicily, Greece and Crete; that there it is usually confined to young children—infantile kala-azar—the parasite of which has been considered a distinct species; and, further, that, whilst in India dogs are seldom affected, in the Mediterranean basin and in Spain very many of these animals are naturally the subjects of leishmaniasis



1, Parasites enclosed in endothelial cells in film from spleen puncture, stained with Leishman. 2, Free forms from spleen. 3, Blood-platelets in same film for comparison. 4, Parasites enclosed within splenic pulp cells, as seen in section, stained with hæmatoxylin. 5, Parasites in histiocytes and endothelial cells in intestinal mucosa. 6, Diagram of Leishman-Donovan body, highly magnified.

LEISHMAN-DONOVAN BODIES IN KALA-AZAR

PLATE VI x 1,000

(L. caninum), and in most cases are closely associated with the infantile human disease.

Adler and Theodor have stressed differences between Mediterranean and Indian kala-azar; in the Mediterranean, children under one year are attacked, while in India kala-azar in infants is uncommon. (It must not, however, be thought that Mediterranean adults are always immune.) In the Mediterranean area it is a seasonal disease both in infants and in dogs. On the outskirts of towns and villages it usually appears in April but is very rare after November. In China, too, it has been observed that children are infected solely in the sandfly season. Thus, if a child be born in October, the first signs may be observed in the following August.

Nicolle differentiated the parasite, which is morphologically indistinguishable from *L. donovani*, as *Leishmania infantum*, but Brumpt considered that this type is normally a parasite of the dog. The resistance of *L. infantum* to antimony therapy was remarked upon by Adler.

This close association between the canine and human disease is not invariable; dogs are commonly found infected in Morocco, where human kala-azar is very rare; in Teheran (Persia) the canine disease is very common: the human disease unknown.

Probably, however, the canine form is more widespread than formerly supposed; in China, for instance, it has been found in Peking as well as in Manchuria (see also Appendix, p. 913).

Infected dogs can be recognized by their extreme emaciation, and thickened and ulcerated skin.

Even in India kala-azar occurs amongst infants and Napier has reported it in a child less than eight months old. In Bengal the peak of ageincidence is eighth to tenth year in girls and from tenth to twelfth year in boys.

Kala-azar may suddenly break out where previously unsuspected. Thus, Schretzenmayr described a sudden outbreak at the beginning of 1938 amongst Chinese troops in Canton, where the disease had not been previously noted. The first case was diagnosed through the discovery of leishmania in a malaria patient, and during the next five months a further 83 cases were identified. The disease appeared to follow the usual course, but in a number of cases jaundice was a feature. Sudden outbreaks have also been recorded in Nigerian troops in Northern Kenya and Southern Abyssinia during the recent war. One half of patients admitted to hospital died.

Ætiology.—The kala-azar parasite (Plate VI) is included by most authorities in the genus Leishmania (though it is morphologically indistinguishable from the genus Leptomonas). Two stages are recognized, intracorporeal and extracorporeal. The parasites grow and multiply within the host cells in the spleen, bone marrow and lymph glands. They are transported along protoplasmic processes which pass from cell to cell. They may also be liberated from disrupted cells and taken up by others. Parasites are also taken up by leucocytes and enter the bloodstream, where most of them are destroyed, although they may survive in numbers sufficient to be detected by blood culture.

Leishman-Donovan bodies are typically parasites of the reticuloendothelial cells. The parasite is a small ovoid or roundish organism measuring 2-4 μ in diameter. When stained according to Leishman's method it shows two lilac-coloured chromatin masses, one larger than the other, enclosed in a cytoplasm having a faint bluish tint about the periphery. The larger is the trophomeleus; the small rod-like body is the rhizoplast. It divides by longitudinal fission.

In smear preparations the parasites are often free or in clusters of various numbers, sometimes arranged with great regularity like the merozoites in the segmenting quartan or tertian malaria parasites. Sometimes as many as 50 to 200, or even more, are found together embedded in a structureless matrix or stroma, the remains of the original host-cell.

The parasite can be cultivated outside the body. The medium used by Rogers was citrated blood. When kept at blood heat the parasites degenerate and disappear, but at a temperature of 20-22° C. they multiply rapidly and assume an elongated motile flagellated form. The flagellum arises from the rhizoplast and projects at the anterior end of the body as in Leptomonas, but there is no undulating membrane as in trypanosomes. These flagellated forms measure 12-20 μ in length, and multiply by longitudinal fission. They move actively, flagellum foremost, and tend to agglomerate into rosette groups with their flagella directed centrally. The N.N.N. medium is now considered the best for culture, but technique must be particular, as bacteriological contamination rapidly kills the parasites. Reichenow's medium of citrated blood and Ringer's solution is also very suitable. A special medium consists of embryonic hamster tissue, heparinized blood, embryonic fluid and spleen extract. Wenyon has succeeded in keeping the parasite alive in successive cultures for fifteen years. The flagellated forms have not been found in the human body, but Wenyon has noted that they may be associated with typical leishman bodies in canine leishmaniasis. The parasite can be communicated to dogs, cats, jackals, monkeys, rats, voles, hamsters and mice, provided that large doses are injected into the peritoneal cavity or into the liver. To infect a dog, it is necessary to inject 2-4 ml. of a thick emulsion of infected spleen, liver, or bone-marrow. Intravenous injection is by no means so successful, while injections of cultures rarely succeed.

It has now been shown that for growth Leishmania donovani and L. tropica require ascorbic acid, hæmatin and also an unknown substance in the serum.

Transmission of the parasite.—Adler (1940) has made some interesting and suggestive observations during attempts to reproduce the disease in five patients with advanced malignant disease by injecting flagellates from cultures and from the organs of infected hamsters. The incubation period was five months, before it was possible to demonstrate the parasites in blood or glands. None of the patients developed marked splenomegaly, fever, or other signs of the disease during nine months. The explanation of this anomaly is not at present forthcoming.

The dog is considered the chief reservoir of infection, but in China, a small rodent, the striped hamster (*Cricetulus griseus*), has proved in the laboratory to be extraordinarily susceptible, and this animal has once been found naturally infected in the wild state. In Morocco a small squirrel (*Xerus getulus*) has also once been found similarly infected.

On account of the peculiar topographical distribution of kala-azar in India Sinton first suggested in 1922¹ that a sandfly (*Phlebotomus*) was the insect vector

and in the same year Napier found a close correspondence between the distribution of *P. argentipes* and the number of kala-azar cases, and noted that this species of sandfly feeds solely on man. A similar suggestion about the leishmania of oriental sore had already been put forward by Wenyon in 1911 and



Fig. 21.—Section of Phlebotomus argentipes, showing pharyngeal infection with Leishmania donovani. (From Indian Jl. Med. Res.)

P, lumen of pharynx; P2, posterior termination of pharynx; T, ridges of crinkly portion of pharynx; M, muscles of pharynx; F, flagellate near anterior extremity of pharynx: F2, flagellates anterior to crinkly portion; F3, flagellates breaking free from main mass of growth; F4, massive growth of flagellates at posterior end of pharynx.

subsequently proved correct by the Sergents in Algiers. Since then a large amount of work on the subject has been performed by Christophers, Shortt, Knowles, Napier, Barraud, Lloyd, and Smith, with the result that a very rapid, intensive development of herpetomonas forms was found to occur in one species of sandfly—Phlebotomus argentipes—when fed on the blood of patients suffering from kala-azar. The whole midgut becomes infected and in some individual

insects the infection spreads to the pharynx, and even to the buccal cavity (Fig. 21). Subsequently it was found possible to transmit the infection to hamsters by artificially infected sandflies in the laboratory and later (1942) Swaminath, Shortt, and Anderson amounced the successful transmission of kalazar by the bites of sandflies to seven human volunteers. This success, after years of fruitless effort, was obtained by sustaining the sandflies during the two weeks of development of the parasite on fruit-juices.

In other endemic centres different species of sandily are involved: *Phle-botomus major* in Eastern Mediterranean; *P. perniciosus* in Western Mediterrean and North Africa; *P. chinensis* and *P. sergenti, var. mongolicus* in China;

P. langeroni in Sudan; and P. intermedius in South America.

An account of the bionomics of the sandtly will be found on p. 1016.

Hu and Cash made the most interesting observation that the leishman bodies are taken up by the cells of the reticulo-endothelial system, or clasmatocytes, and these, in experimentally-infected hamsters, become massed as a thick layer of heavily infected tissue lying immediately underneath the skin, though externally no change can be seen. This observation has been confirmed by Hindle and in skin sections from fatal cases of kala-azar a similar condition has been found. All levels of the skin below the epidermis contain leishmania-filled cells collected in large masses about the sweat-glands and arterioles and scattered diffusely throughout the corium. The relationship between this condition and the curious skin eruptions (p. 15-4) described in India is of interest, and suggests how the parasites may be abstracted by sandtlies.

It had been suggested that the transmission may be direct from man to man through the fæces. The evidence for this is based upon the fact that leishmania parasites occur in polypoid masses in some intestinal cases of kala-azar within the intestinal mucosa. Shortt and his colleagues demonstrated Leishman-Donovan bodies in numbers in blood-and-mucous stools in a boy suffering from kala-azar with dysenteric symptoms.

Forkner and Zia in China, on the other hand, discovered leishmania in material obtained by passing a swab over the nasal mucosa of nine kala-azar patients, and parasites were also seen in the material blown from the nose (droplet infection). The tonsils were heavily infected. Material from these situations

produced kala-azar in hamsters by intraperitoncal inoculation.

Shortt and Swaminath also reported Leishmania donovani in the nasal mucus from cases of Indian kala-azar. In a certain proportion of advanced cases viable

parasites are also excreted in the urine.

That kala-azar may occasionally be a congenital infection has been suggested by Carmichael Low and Cooke (1926), who diagnosed this disease in a child seven months old, born in England of a mother who suffered severely from kala-azar during pregnancy. The fact that leishmania is a tissue parasite makes it easier to understand the mechanism of congenital kala-azar than that of congenital malaria. Two cases transmitted by blood transfusion have been reported by Chung.

Predisposing causes.—Kala-azar attacks both sexes and all ages but shows a predilection for recently arrived immigrants. In the Mediterranean basin it occurs almost, though not quite, exclusively in children (five months and upwards): in India it occurs at any age.

Pathology.—The spleen is grossly enlarged. In the acute stage the capsule is smooth, thickened and nodular, becoming in the chronic form almost cartilaginous. The splenic pulp is increased in amount and very friable. There are usually numerous infarctions. The hypertrophy is due to congestion and reticulo-endothelial proliferation; it is estimated that a considerable part of the spleen substance is composed of parasites. There is little fibrosis. The leishmania are numerically more abundant in the spleen than in any other organ.

The liver is also enlarged, brown or mottled, almost nutmeg in appearance. The Kupffer cells are packed with parasites. There is some pressure atrophy of the parenchyma cells and, finally, in the chronic stage, a fine intralobular cirrhosis.

The bone-marrow is reddish, containing abundant parasites; the destruction may be so extensive that very little blood-

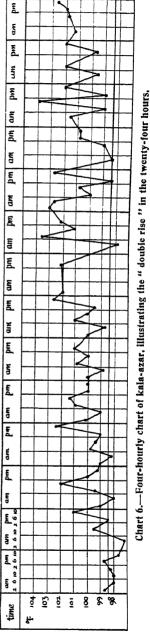
forming tissue remains.

The kidneys contain few parasites, which are carried there by the bloodstream. Those scanty parasites which have been found in the urine are probably derived from invasion of the bladder.

The lungs show no parasites, but are liable to secondary bacterial invasion on account of the leucopenia which is such a constant feature of this disease.

In the gastro-intestinal tract there is proliferation of reticulo-endothelial cells, especially in the duodenum and jejunum. The villi may become grossly hypertrophied and swollen by packed parasitized cells. Small ulcerations are not uncommon and parasites can be demonstrated in them.

The lymphatic glands are generally enlarged and congested, especially the mesenteric group, and the tissue is usually invaded by large numbers of leishmania. There is also hypertrophy of the retro-pharyngeal lymphoid tissue, and



Leishman bodies can be found in nasal and pharyngeal secretions.

The underlying essential pathology of this disease is blockage of the endothelial system (Hu and Cash). The parasites are engulfed by the endothelial cells; they then multiply until the cell ruptures and the organisms, escaping into the bloodstream, are transported to other organs.

Symptoms.—The incubation period is difficult to fix. In one Englishman under Manson's care the time that clapsed from his arrival in perfect health in the endemic region and the onset of fever which terminated in kala-azar (diagnosed microscopically both before and after death) was under ten days. Kirk, on the other hand, from accurate observations in the Sudan, fixes the period between three and six months, but it may be as long as two years (Sweeney, 1945). In some artificially-infected dogs, the disease, like dermal leishmaniasis, may remain latent for months.

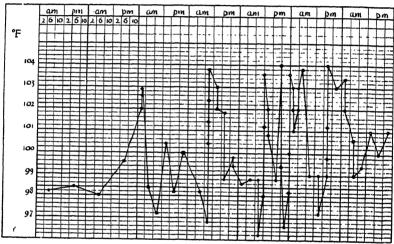


Chart 7.—Temperature chart of acute kala-azar, showing "double crisis." (Dr. G. Carmichael Low.)

A primary lesion in the form of one or more minute dark red papules on the face was described by Mirzoian in Central Asia.

The onset may be gradual or sudden; if gradual, it cannot be diagnosed at all on clinical grounds. If sudden, there is usually high fever, which may be preceded by rigor and, in some cases, by vomiting. The initial fever may be very severe (Charts 6, 7). It is intermittent in some instances, more frequently remittent, often with a double remission in the twenty-four hours, resembling that of subtertian malaria. It lasts from two to six weeks, occasionally longer. Waves of fever, separated by apyrexial periods, may often simulate undulant fever, and during the pyrexial periods both the liver and the spleen enlarge. There may be daily rigors, so that malaria may be suspected. A four-hourly temperature chart in a well-marked case may show a double or even a trip'e rise of fever.

It is now generally accepted that, though the underlying clinical picture is basically the same, there exist different clinical types and that the

leishmania parasites vary considerably in virulence and in resistance to treatment. The Indian and Eastern forms are on the whole less deadly than the Sudanese or that encountered during the war in Southern Abyssinia and in Northern Kenya. The infantile Mediterranean form also appears to be a distinct clinical entity. Rarely the full clinical picture may not be developed. In soldiers who contracted the infection in North Africa and Sicily in 1948 some showed enlargement of the lymphatic glands, particularly of the cervical group, associated with complete freedom from other signs and symptoms. On the other hand, some of the Southern Abyssinian cases were extremely severe. A nodular rash developed which coalesced to form warty masses in which parasites were demonstrated.

The clinical picture.—The spleen is usually enlarged from the commencement of the illness, whilst the liver does not become appreciably bigger until the disease has lasted some months, but in rare cases in the initial stages, enlargement of the spleen may not be an outstanding feature. The Editor has treated cases in which hepatomegaly persisted for some months before the spleen became palpable. Generalized lymphadenitis is common, and in China and in Brazil, uniform enlargement of the cervical glands has been observed. In India, too, cervical adenitis may sometimes occur, and occasionally, too, there is enlargement of the epitrochlear glands.

Then comes a period of apyrexia and general improvement, to be fellowed once more by fever, splenic and hepatic enlargement, and perhaps tenderuess. In women amenorrhoea is often an early symptom. In this way spells of fever and apprexia recur for months, absolutely unchecked by quinine, until finally a low form of fever, rarely over 102° F. becomes more or less persistent. sweats are common during remissions at all stages of the fever; in the more chronic rigors occur exceptionally. Pains in the limbs often suggest rheumatism. When the disease is thoroughly established, emaciation and anæmia become noticeable, and, together with the enlargement of the liver and spleen, produce a typical appearance. Edema of the legs, sometimes circumscribed, may be present. In many cases the skin acquires a strange earthy-grey colour; this dusky pigmentation, which has given rise to the



Fig. 22.—Kala-azar in Indian boy. (Col. L. E. Napier.)

native name, kala-azar, "the black disease," is best seen on the feet, hands and abdomen in Europeans, though very difficult to distinguish in dark-skinned natives. The hair is apt to become dull, dry, and brittle, and may fall out; petechiæ, in the axillæ especially, are not unusual; epistaxis and bleeding from the gums are common. This condition

of chronic fever, enlargement of spleen and liver, emaciation, and anæmia may continue for months or even one or two years, until improvement sets in. More usually—96 per cent. of cases (Rogers), 150 recoveries in 2,000 cases (Price), 24 recoveries in 100 cases (Lignos)—the patient is cut off by some intercurrent disease, especially dysentery.

One outstanding clinical feature is that, in spite of the patient's weak. emaciated condition, the pyrexia, and the protuberant abdomen due to splenic enlargement, he preserves a good appetite and a clean tongue; he may be working with a temperature of 102° F. quite unaware that he has fever (Fig. 22). There is no malaise or apathy. In this respect kalaazar differs from malaria and other toxic fevers, such as typhoid. Kala-azar usually lasts several years, but the Sudan cases, especially, may run an acute course in about five months. In the terminal stages ascites may develop, due to gradually increasing circhosis of the liver. Anemia may become progressively severe. Hæmic murmurs of the heart are often heard. Hemorrhages may occur from any part of the body, and purpuric patches may appear on the skin after local injury. Death may ensue from several causes. When due to the disease alone it results from exhaustion. Dysenteric symptoms are frequent, and may be due to intestinal lesions caused by Leishman-Donovan bodies, or to a superadded infection with amcebic or bacillary dysentery. Broncho-pneumonia and noma are frequent terminal symptoms. Proctor, however, reports that noma can be arrested in the early stages by scrupulous daily inspection of the mouth. Should a grey line of ulceration on the gums be seen, it should be energetically treated with carbolic acid and spirit. It may be that this gangrenous process is not so much due to the kala-azar as to the leucopenia, and it has a striking analogy in the angina which is characteristic of agranulocytosis.

Blood changes.—Ancenia is invariable in advanced cases and is due to destruction of the erythroblastic tissue of the bone marrow. These changes are not so obvious in the infantile form. The red blood corpuscles are often reduced to 2,500,000 per cu. mm. with a corresponding

and parallel fall in hæmoglobin.

The most remarkable change is leucopenia. The leucocytes are reduced below 3,000 per c.mm. in 95 per cent. of cases; below 2,000 in 73 per cent.; and 1,000 in 42 per cent. The proportion of leucocytes to erythrocytes, normally 1 to 750, stands at 1 to 1,500 or even 1 to 2,000. The differential count usually shows a relative increase of lymphocytes, a moderate increase of large mononuclears and almost complete absence of eosinophiles. (The biochemistry of the blood is described on p. 158. Owing to the increase of euglobulin in the serum, Henry's reaction is usually positive.) The liability of kala-azar patients to pneumonia and superadded septic infections is ascribed to leucopenia.

The reduction in leucocytes may proceed to acute agranulocytosis.

Acute toxic kala-azar.—When kala-azar breaks out in a new area, especially in the stress of war, it may assume an acute and almost unrecognizable form. This happened in Nigerian regiments during the 1940-41 Abyssinian campaign, as reported by Cole, Cosgrave and Robinson.

The case mortality-rate of one outbreak was almost 50 per cent. The onset was sudden, often with rigors, headache, epistaxis, high fever, abdominal pain, vomiting, painful liver and spleen. In a proportion of cases the course of the disease was so rapid that the spleen never became palpable. Renal symptoms were noted, whilst the urine contained albumin and casts. The complications were hæmorrhagic: bleeding from gums, skin petechiæ, and blood-and-mucous stools. (Œdema was noted in three cases, and in three there was general anasarca (Cole, 1944).

Infantile kala-azar.—This occurs typically in Malta where it has been graphically described by Debono. The youngest case was 4 months old, in the majority the age is 1-2. There are important bone-marrow changes in which the hæmopoietic elements are crowded out by proliferating endothelium, but the myeloblastic tissues suffer to an even greater extent, so that leucopenia is always a prominent feature and agranulocytosis is apt to supervene. This is responsible for the great liability to secondary infections and cancrum oris. The blood platelets are reduced to 100,000, so that thrombocytopenia results in hæmorrhagic purpura and ecchymoses. The incubation period is usually three to four months. In children under two the onset is acute with hyperpyrexia and vomiting. Untreated it is invariably fatal. In older children it runs a subacute course lasting six to eighteen months. The course of the disease may be cut short by bronchopneumonia or cancrum oris. Sudden death may be due to hyperpyrexia, vomiting, intense dyspnæa or hæmorrhage. A double crisis is common, one at 11 a.m. and the second during the evening, followed by sweating in the early hours of the morning. Fair children develop pallor rapidly with slight generalized cedema suggesting subacute nephritis. The lymphatic glands are usually enlarged. Splenic puncture is regarded as the most reliable test, but on account of the danger, blood culture performed with meticulous technique is preferable. The formolgel, antimony and other biochemical tests are not usually reliable before the fourth month of the illness. The clinical picture may resemble that of splenic anæmia (Banti's disease) very closely.

Dermal leishmanoid.—A cutaneous form of leishmaniasis, in which the parasites occur in nodules in "butterfly patch" formation on face, forearms, inner aspects of thighs and pubic regions, was first reported by Christophers in India in 1904, and Thomson and Balfour in the Sudan in 1909, and has since been observed in the Blue Nile (Kassala) districts. It was described by Brahmachari in India under the name of "dermal leishmanoid," or "post-kala-azar leishmaniasis." No cases have been recorded in the Mediterranean. It is certainly a sequel to generalized infection with L. donovani, as more than half the patients who exhibit this curious eruption had suffered from kala-azar about one year previously and had been given antimony treatment. In Bengal 5 per cent. of patients so treated have developed dermal leishmanoid. The leishmania are found in smears from the nodules, and cultures have been obtained from the lesions. It is not at all clear at present what the significance of this phenomenon is, or what factor causes the organisms to establish themselves in the skin. This condition occurs in all classes of the community, in persons of all ages and both sexes. Antimony appears to be specific, but cure is not so rapidly effected as in the visceral form. Stilbamidine is useless.

The first, or depigmented, stage usually appears as colourless patches on the face and upper extremities, gradually spreading to the remainder of the body. Minute dots gradually enlarge to irregular areas half an inch in diameter, which



Fig. 23.—Dermal leishmanoid. Extensive nodular lesions on face and ears. (Acton and Napier, Ind. Jl. Med. Res.)

occasionally tend to break down. There is cedema of the subpapillary tissues accompanied by dilatation of the vessels. Below this there is infiltration by macrophages of the subpapillary plexus. The second, or nodular stage, is seen about two years after antimony treatment. (Fig. 23.) Usually the nodules replace the depigmented patches, but there are certain areas, such as the face, where the nodules appear much earlier than in other parts of the body. They may extend to the mucous membranes and ears, and may closely resemble leprosy. In the Sudan a punctate cutaneous cruption has been described by Kirk, and in the larger nodules leishmania can be demonstrated, especially towards the completion of antimony treatment. The epithelium is thin and the subpapillary

layer is edematous, with atrophy of the fibrous and elastic tissue. Subjacent to this edematous area is a granulomatous mass consisting of proliferating macrophages. There is also a xanthomatous form. These lesions are raised, orange-coloured plaques which are painless and do not ulcerate.

Preliminary treatment with massive doses of potassium iodide causes the nodules to ulcerate and they then become susceptible to intravenous injections of

urea stibamine (see p. 160).

Association of kala-azar with oriental sore.—It was formerly considered that these two clinical entities were never associated, but this appears to be by no means invariable. Originally Christopherson, Kirk and Macdonald in the Sudan, described cases where visceral, cutaneous, and even mucosal lesions are present in the same individual. In China, too, Wang found subcutaneous nodules, composed of endothelial cells with many leishmania. In the Sudanese form of kala-azar circumscribed cutaneous ulcers with a tendency to coalesce are the most frequent.

In discussing the evolution of leishmania infections in man Kirk considers that no hard-and-fast line can be recognized between the three

types.

Eye lesions.—R. E. Wright showed that when eye lesions occur in kala-azar, as in malaria, they are due to retinal hæmorrhages in the posterior segment of the eye.

Immunity.—There is no definite evidence of the mechanism of immunity to kala-azar. It has been shown that immunization against bacterial infection is not interfered with by the blockage of the reticulo-endothelial system which results from generalized leishmania infection.

Noguchi was able to demonstrate differences in antigenic structure between L. donovani, tropica and braziliensis, but that L. infantum and L. donovani were antigenetically identical. Some strains of L. caninum are closely related to L. donovani. Complement-fixation antibody was demonstrated by Hindle, using an emulsion of the flagellate stage as antigen.

Diagnosis.—Irregular chronic fever with enlargement of the spleen and diminution in the number of leucocytes in patients from the endemic zone suggests kala-azar. Examination of the blood can at once exclude leucocythæmia and also malaria, if taken together with absence of tertian or quartan periodicity and the inefficacy of quinine, atebrin or paludrine. Sometimes in early infections diagnosis is very difficult, when Leishman-Donovan bodies cannot be found, the formol-gel test is negative and leucopenia is absent.

Splenic puncture must not be lightly undertaken. A preliminary examination of the blood should always be made to ascertain the degree of anæmia, to exclude leucocythæmia and to obviate the necessity for splenic puncture, and the attendant risk of fatal hæmorrhage so easily induced in that disease. Liver puncture.— When the liver is enlarged, it should be punctured instead of the spleen as it is less vascular and less easily torn, but, as a general rule, the parasites are not so abundant and the results are therefore unsatisfactory. In performing puncture, the abdomen should be firmly fixed with a binder to prevent, as far as possible, movement of the diaphragm and consequent risk of tearing the punctured organ. The patient should be injected with $\frac{1}{10}$ gr. of atropine one hour previously

and the puncture site infiltrated with novocain to deaden pain. It is wise to give 30 gr. of calcium lactate the evening before and on the morning of the puncture. The lower border of the splcen or liver should be steadied by the hand. A hypodermic needle, scrupulously clean and dry, and connected with the barrel of the syringe by a short length of rubber tubing, should be used, the patient being directed not to start or breathe when the puncture is being made. The type of needle is most important. The bore should be neither too big nor too small. The Editor has found Maw's size No. 10, with a shaft 40 mm. in length, the most suitable, and Napier has devised a special spleen-puncture syringe (Fig. 24). The patient should hold his breath in full inspiration whilst the needle is in the spleen. He should be given nothing by the mouth for at least two hours before puncture. He should lie supine on the left side of the bed and the operator should stand on his left side. The skin is infiltrated with 2 per cent. procaine hydrochloride solution. Local anaesthesia is continued up to the peritoneal layer with 20 gauge needle. Failure to draw blood is not to be

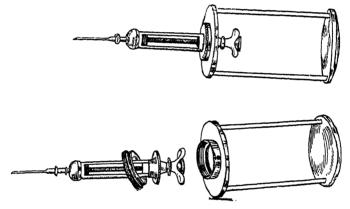


Fig. 24.—Spleen puncturing syringe. (After Col. L. R. Napier.)

regarded as failure to obtain material for microscopical examination; on the contrary, it is an advantage, as the object is to procure spleen or liver pulp, not blood. After the contents of the needle have been blown out on a slide, it may be trans-illuminated by an electric pocket-torch to discover the minute sago-like masses of splenic tissue. A film should then be spread and, after it has dried, stained by Leishman's or Giemsa's method, and then examined with a $_{1^12}$ in objective. Adler points out the desirability of culturing the material obtained on suitable media, as the parasites may be so few as to be missed by examination of smears.

Splenic puncture is not advisable in infants on account of the danger of laceration and intraperitoneal hæmorrhage. For puncturing the liver the site of election is the 7th or 8th intercostal space in the mammary line.

Lymphatic gland puncture is efficient and simple (Kirk and Sati), generally most efficacious in the glands of the groin. The lymph is massaged into the needle, into which it runs by capillary attraction. The skin is sterilized, and the glands identified, pulled up from the underlying tissues and steadied by juxtaposition of the index finger and thumb. A dry sterile needle (hypodermic 16) is pushed through the skin into the gland; and it is easy to feel when the needle

¹ A trace of water in the needle will distort or burst the parasite and render it unrecognizable.

has entered. It is held there for a second or two, then quickly withdrawn and attached to a small syringe, by which the gland "juice" in the needle can be blown on to a slide and stained by Leishman stain.

Sternal puncture was advocated as a diagnostic procedure by Lovando in Athens, by Andrew Ura, Regli, L. Brumpt and Benhamou. It is safer and surer than spleen puncture, and Chung in Peking considered it the best method, and that a local anæsthetic is seldom necessary. A shortened lumbar puncture needle is inserted at an angle of 30 or 40 degrees at the level of the second or third interspace. The needle, with contained stylet, is pushed with a boring action through the bony lamina. When the marrow is reached, the stylet is removed and a syringe for aspiration attached. Even in the absence of parasites, a myelogram is said to be distinctive. The average is: granulocytes 23, erythoblasts 24, hyaline leucocytes 53. Normally granulocytes are four times as numerous as erythroblasts and 3.5 times as hyaline leucocytes.

Bone puncture.—Giraud considered tibial puncture the method of election in young children. The point selected is the inner surface of the tibial epiphysis, 1 cm. below the knee joint. A fine trocar and cannula is passed until entry into the spongy tissue is signalized by loss of resistance. The bone marrow changes indicate regenerative action of the normoblastic type and inhibition of myeloid cells (see above). The material should be sown on appropriate media in every case, as parasites are usually too few to detect in smears.

Blood examination.—The frequency with which this parasite has been found by blood examination varies in different localities. In some places, as in Madras and Assam, Leishman-Donovan bodies are evident in about 60 per cent. of all cases examined, enclosed within large mononuclear cells, and to a lesser extent within polymorphonuclear leucocytes.

Knowles and Das Gupta used thick films, prepared by placing four drops of blood on a slide, mixed so as to cover an area of $\frac{1}{4}$ sq. in. The film is covered with a Petri dish and dried at 37° C. for two hours. It is then flooded with glacial acetic acid (2·5 per cent.), 4 parts, crystalline tartaric acid (2 per cent.), 1 part, for five minutes. After tilting off the fluid, the film should be fixed with methyl alcohol and covered with dilute Giemsa stain. It is claimed that by this method leishmania can be found in 67 per cent. of cases.

Shortt and his colleagues place a small drop at one end of a slide with a second one applied in the usual manner, and spread a thin film. At this stage the spreading slide is abruptly lifted, so that the blood-smear ends in a straight edge which is somewhat thicker than the rest of the smear.

Young and Van Sant obtained good results by centrifuging 5 ml. of blood in Locke's solution (modified) (sodium chloride 9 grm., potassium chloride 0.4 grm., calcium chloride 0.2 grm., sodium citrate 10 grm., distilled water 1,000 ml.) at a speed of 750 revolutions. The parasites are readily discovered in films from the bottom of the centrifuge-tube.

The presence of the parasite in the peripheral blood can be verified by blood-culture. For this purpose 2 ml. of blood are drawn off by means of a 2-ml. syringe, and mingled with 1 ml. of 6 per cent. citrate solution in a sterile tube; this is placed in a cool incubator and allowed to sediment for two hours. The deposit is drawn up by a pipette, inoculated into two or more tubes of N.N.N. medium, and placed in a cool incubator. Examination of cultures is made about the tenth day, when flagellate

forms are observed, but observation must be continued for at least twenty days. Splenic pulp may be cultured in the same manner.

Biochemical reactions.—The alkalinity of the blood is said to be decreased, while in some cases the coagulation-time is very considerably prolonged.

A specific complement fixation test was introduced by Niyogi and Ray (1942). The antigen is prepared from washed flagellates from 48-hour cultures of L. donowani: 60 millions per ml. was found to be reliable. The suspensions were shaken for 48 hours in a machine and then kept in a refrigerator.

Aldehyde, "formol-gel test" (or the serum-formalin reaction (Brahmachari and Napier) proved to be very useful as a method of diagnosing kala-azar on a large scale. About 5 ml. of blood is withdrawn from a vein and allowed to stand a sufficient time for the serum to separate; 1 ml. of clear serum is then placed in a test-tube (3 by 1 in.), and to this I drop of 30 per cent. formaldehyde, or commercial formalin, is added. The serum is at once well shaken and placed in a test-tube rack at room temperature. In a certain proportion of cases of kalaazar, especially in chronic cases, solidification of the serum takes place within a space of three to twenty minutes, but a control of normal serum should always be made. Napier himself states that "jellification" with opacity (like the white of an egg) of the serum may be taken as diagnostic of kala-azar, if the disease is of more than three or four months' standing, but milkiness without solidification only takes place in early cases. But in exceptional cases even this reaction does not become apparent until an advanced stage. Should the serum be hamoglobinstained, this will change to chocolate brown after twenty-four hours. In certain cases of syphilis, leprosy. hepatic cirrhosis, schistosomiasis, subacute endocarditis, lymphadenoma, phthisis, and malaria the serum will solidify, but remains clear and does not become opplescent as in kala-azar. The reaction, which occurs in twenty minutes, is given as ++++; after two hours as +-|, and after twenty-four hours as +.

Other so-called lability reactions are also positive, as for instance, the Takata-Ara which is used for the diagnosis of liver cirrhosis and other diseases with increase of globulin in the blood: $0.02~\mathrm{ml}$, of blood is mixed with $0.6~\mathrm{ml}$, of distilled water. Haziness or cloudiness develops after five minutes and the globulin test is positive; after fifteen minutes a distinct precipitate occurs. The distilled water must be neutral with pH varying between 7 and 7.2.

In kala-azar it has been proved that the plasma globulins are increased, while the albumins are diminished. In kala-azar, the albumins are 2.8; the globulins 4.0, as compared to 4.5 and 2.0 per cent. respectively in the normal. Lloyd and Powell constructed a typical globulin curve of kala-azar in which euglobulin constitutes 40-50 per cent. of the total. Auto-agglutination of the red blood-corpuscles is often noted, as in trypanosomiasis, more especially in advanced cases. The thymol turbidity test of Rangue consists of the addition of 0.05 ml. of serum to 3 ml. of saturated solution of thymol buffered to pH.7.8. Readings are made with a Vernes photometer and a green screen after thirty minutes. Complement fixation (Chung) is of diagnostic and prognostic importance. The antigens are prepared from spleen and livers of infected voles and hamsters.

Antimony test.—Chopra pointed out, and Napier confirmed, the curious fact that the addition of a 4 per cent. solution of pentavalent antimony compounds to kala-azar serum causes a heavy precipitate, the amount of which corresponds to the efficacy of that compound in the treatment of the disease.

The method is as follows: One to two drops of blood from the pricked finger are allowed to flow into a Dreyer's tube in which has been placed 0-25 ml. of ¹ The Bramachari reaction or "ring test" consists of one part of patient's serum to two parts of distilled water when a ring forms. It is also non-specific.

a 2 per cent. potassium acetate solution. The tube is then inverted to mix the contents; a little of this mixture is transferred to another tube, and a 4 per cent. solution of the antimony compound (stiburea, for example) is added by means of a capillary pipette and allowed to percolate along the wall, so that it comes to lie below the blood mixture. In a positive case a flocculent precipitate forms at the junction. In very early cases it may not appear for 10-15 minutes: in the more advanced it is immediate. The character of the precipitate is important in kala-azar; it is so flocculent that it is not easily broken up by shaking, and it does not disappear in twenty-four hours.

In cases of doubt it is a good procedure to dilute the serum with 10 volumes of distilled water and to repeat the test. Alcohol must not be used for cleansing the finger. André (1932) claimed that the results are improved by reading the opalescence produced in kala-azar serum by urea stibamine by means of the

"Vernes-Bricq-Yvon" photometer.

Napier stated that the aldehyde and antimony tests are almost of equal value. Out of 201 cases of kala-azar diagnosed by discovery of the parasite, 156 gave a positive antimony test, and 128 the aldehyde test.

Differential diagnosis has to be made from splenic anæmia, bacterial endocarditis, cirrhosis of the liver, trypanosomiasis, and Egyptian splenomegaly (Schistosoma mansoni) which, save for the absence of the parasite and the characteristic pyrexia, may closely simulate kala-azar. Visceral syphilis, with enlargement of liver and spleen, malignant disease and tuberculosis of the spleen, may have to be excluded. In China and Japan kala-azar may have to be differentiated from intestinal schistosomiasis (Schistosoma japonicum), in which enlargement of the abdominal organs may occur. The remarkably clean tongue and the good appetite serve in some measure to differentiate kala-azar from chronic malaria, to which may be added the considerable emaciation, absence of extreme anæmia, double daily rise of temperature (in 88 per cent. of cases), distension of the superficial abdominal veins, and pigmentation of the extremities.

TREATMENT

Antimony treatment.—The reaction of a kala-azar patient to antimony treatment can be assessed in various ways: in improvement in the clinical condition, increase in body-weight, shrinkage in size of the spleen and of the liver, and increase of the leucocyte count. The relative proportion of serum globulin can be gauged by the aldehyde test, which is positive so long as the parasites remain active in the body and, moreover, persists for two to three months after the patient has, to all external appearances, completely recovered.

Even in cases reacting favourably to treatment, it is stated that apparently unchanged and viable parasites may be found in the spleen even after a gramme or more of antimony preparations has been injected, but by the time the spleen has retracted within the costal margin, the Leishman-Donovan bodies have

disappeared altogether.

compounds οf antimony.— 1. Treatment with pentavalent (a) Neostibosan is the amino salt of para-aminophenylstibinic acid, contains 40 per cent. of metallic antimony, and is comparatively non-toxic. It may be given in a strength of 25 per cent., either intravenously or intramuscularly. doses may be given daily, but generally speaking, alternate days are preferable. The initial dose for an adult is 0·1 grm., the second 0·2 grm., the third 0·3 grm. This compound appears to be especially well tolerated. About ten injections are required for an average case, and a total of 2.7-4.0 grm. is usually necessary to effect a cure.

It has been pointed out by Neumann that in Malta, quite apart from the difficulties in administration, intravenous injections of antimony in children are apt to be followed by broncho-pneumonia, but neostibosan, when given intramuscularly, is almost equal in effect to the intravenous method. A dose of 2.5 grm. suffices within a period of six weeks. Debono, on the other hand. favours injection into the jugular vein in small children and considers the intramuscular method less satisfactory, and that by this method absorption is poor. The initial dose of neostibosan is 0.05 grm., increased by another 0.05 grm. (or 0.025 grm. in infants under one year) until limit of tolerance as shown by vomiting. The course is one of 16 injections. The average total dose is 0·1-0·15 grm, in babies under a year; 0.2-0.25 grm. under two years, and 0.3 grm. in older children. If after two months the spleen is still enlarged and Leishman-Donovan bodies present, a second course of higher dosage is advisable. Blood transfusions are necessary when the hæmoglobin is under 40 per cent. Penicillin has no effect on the Leishman-Donovan bodies, but is invaluable in treatment of intercurrent broncho-pneumonia.

(b) Urea stibamine,—aminostiburea, carbo-stibamine, carbantine—(stiburea— $C_7H_{12}O_6N_2Sb$), is a compound of urea with stibamine (p-aminophenylstibinic acid), and was introduced by Brahmachari. This compound is apt to undergo chemical changes if exposed to the air. Urea stibamine is undoubtedly an efficient preparation and often succeeds where other pentavalent salts fail; in resistant cases it may be given in combination with neostibosan; and the Editor has seen successful results from this method. The total amount to effect a cure is about 3 grm., and the usual length of treatment is one month; if, for some reason or other, intermission in treatment takes place, the parasites tend to become antimony-fast. Urea stibamine may be given intramuscularly to infants in doses from 0-01–0-08 grm. in 1–2 ml. distilled water, a total of 0-05 grm. being necessary.

(c) Solustibosan 561 (pentavalent antimony gluconate) was introduced by Kikuth and H. Schmidt who considered it in many ways superior to neostibosan in the treatment of kala-azar. It is issued in ampoules of sterile isotonic neutral solution in water so that 1 ml. contains 20 mgm. of antimony; thus 6 ml. correspond to 0·39 grm. of neostibosan and contain 0·120 grm. of antimony. It can be given intramuscularly or intravenously. The initial dose is 6 ml. for sensitivity test. Thereafter it is 12 ml. daily, or on alternate days, up to a total of 120 ml. for an adult of 60 kg. weight. On account of the danger of allergic reactions it is advised that a break of ten days should be made between the fifth and sixth injections, if any untoward symptoms are observed. Neostam (B.W.) is a similar preparation. Pentostam (sodium antimony gluconate) has been used by Tuckman in Chinese kala-azar. The total dosage is 9 ml. for a child of 10 kg. and 30 ml. for adults of 50 kg. or over. This preparation is non-toxic.

Stibatin (Glaxo) is supplied in rubber-capped bottles containing 20 mgm. pentavalent antimony per millilitre. The doses advised are two 4-ml. and nine doses of 6 ml. on alternate days, with a total dosage of 60 ml. In young children the injection is best given intramuscularly. Castanys (1945) recommended an oily suspension of antimony hexonate for the treatment of the infantile form in children of 7 months to 3 years. The total administered intramuscularly varied from 10 to 19 ml. This quantity was given in ten daily injections, or in seven injections on alternate days.

Toxic effects of antimony treatment.—Christopherson stated that "metallic taste in the mouth and throat need scarcely be considered as poisoning, but vomiting, giddiness, delirium, a considerable rise or fall in temperature, diarrhœa, and cramp in calves should be taken

seriously. They are danger signals and, when they occur, the injections should be temporarily suspended. Rapid pulse, cold, clammy skin, signs of collapse, in fact, are serious symptoms of poisoning." Discomfort or pain in the chest, colic, headache, severe arthritic pains in shoulder and other joints, bone pains, especially in the shins, and even jaundice may be noted.

Disagreeable symptoms are less likely to ensue since the introduction of the pentavalent salts of antimony. The death-rate among kala-azar patients has undoubtedly been much reduced by their use (42 per cent. in 1925, according to Napier). Jaundice is, perhaps, more common.

2. Diamidino stilbene (stilbamidine).—The Mediterranean and Sudanese forms of kala-azar have proved more refractory to antimony treatment, requiring on an average double the amount necessary to cure the Indian strain.

Napier and his colleagues (1942) published results in a series of 100 Indian patients to whom stilbamidine was given intravenously in 1 per cent. solution. They concluded that the introduction of stilbamidine constituted a great advance in the treatment of kala-azar. Antimony-resistant cases responded particularly favourably. Weight for weight, only about one-quarter as much stilbamidine is required per case as neostibosan: 60 grm. suffices to cure 100 patients. The drug is apparently of no value in the treatment of dermal leishmanoid or cutaneous leishmaniasis.

It should be dissolved in 10 ml. of water and injected very slowly, otherwise it may cause vomiting. Administration is followed by a very considerable fall in blood pressure and also by a temporary decrease in blood sugar. The patient becomes flushed, with a burning sensation in chest and abdomen and slight dyspncea, probably the result of stimulation of the parasympathetic system; these effects can be mitigated by adrenaline.

A disadvantage to the extensive application of stilbamidine has been the supervention of neuropathies, sometimes as long as three months after the cessation of treatment, possibly from the action on the basal ganglia, producing anæsthesia of the head and neck. Napier reported that in half of his patients subjective disturbances of sensation ensued, such as hyperæsthesia, paræsthesia, anæsthesia, loss of sensation to light and touch, preservation of pressure sense and pain. In some these disturbances are transitory, in others they appear to be permanent. Epileptiform seizures have been reported by Kirk and Sati (1940).

Pentamidine isethionate (or lomidine) is now used in place of stilbamidine and does not produce such disagreeable after-effects. The doses are the same as employed for the treatment of trypanosomiasis (p. 129). The dose for adults is 180 mgm. on the first day increasing to 200 mgm. for 7–10 injections. Hazarika (1949) in 55 cases gave 10 per cent. solution of pentamidine intravenously in 25 and intramuscularly in 28; 10–20 injections were given and the total relative dose (per 100 lb. weight) ranged between 0.6 and 3.0 mgm. Vasomotor-symptoms constituted the side-effects. Ghosal and Sinha (1948) gave pentamidine intramuscularly on consecutive days in 10 per cent. solution: 1 ml. for the first, 1.5 ml. for the second and 2 ml. for subsequent doses. The temperature fell to normal after 5–6 injections.

Splenectomy in Kala-azar.—Nicolle and Compte in 1910 performed splenectomy in a dog but it had no effect upon the course of the disease. In the same year, Alvares in Lisbon did splenectomy in a boy of 9. Though he recovered from the operation, he continued to harbour parasites in the liver. Similar results were obtained by Makkas in Athens, but in 1916 Kokoris reported the successful cure of a child of 3 in Greece. Cochran

(1915) in the Chinese form, reported two successful cases in adults, and hæmorrhage was forestalled by the transfusion of 50-60 ml. of healthy blood. There was immediate marked increase of haemoglobin and absence of leucopenia. Parasites were still present in the liver. In 1930 Timpano had a successful case in infantile kala-azar in Italy. Abrami (1931) also recorded a successful result in Mediterranean kala-azar in a woman of 35. A course of neostibosan and blood transfusion (200 ml.) followed the operation.

Martin, Chorine and Rouessé (1985) reported a similar case from the

South of France.

Burchenal, Bowers and Haedicke (1947) have also recorded successful splenectomy in a negro soldier infected in North Africa. The formol-gel

test became negative on the twelfth week after operation.

Morton (1948) has recorded fully the case of an English soldier infected in Calcutta with kala-azar completely resistant to antimony treatment. The spleen, which weighed $5\frac{1}{2}$ lbs., was full of leishmania. He had a further course of carbo-stibamine, followed in twelve days by a full course of pentamidine. According to Das and Sen Gupta splenectomy does not usually cure these cases.

Prognosis.—Kala-azar is, in the great unjority of eases, a chronic disease; but acute cases are noted in the early stages of an epidemic. Marked intestinal disturbance, ascites and liver cirrhosis indicate a bad prognosis, as does also extreme leucopenia. The prognosis is naturally affected by coincident infections such as malaria, the dysenteries and ancylostomiasis. Napier pointed out that with superadded pulmonary tuberculosis it is especially grave; but there is a tendency to spontaneous cure in about 10 per cent. of cases. The oft-repeated statement that, owing to the introduction of the antimony treatment, a 95-per-cent. mortality-rate has been converted to an equally high recovery-rate, is, therefore, not strictly true.

Prophylaxis.—Domestic and personal cleanliness is of great importance. Infected dogs should be destroyed, and in the endemic districts they should be kept away from association with man. Papantonakis proved that destruction of dogs in Canea in 1938 was followed by marked decrease of kala-azar in the following year. Many years ago by segregating the sick, burning houses, clothing and furniture, and providing new huts, Price, Rogers, and Young succeeded in banishing the disease in parts of Assam. Good results in prophylaxis have already followed the actual treatment of cases on a large scale. Energetic measures against sandflies should be instigated. This involves protection against sandfly bites and the control of sandfly breeding places by DDT residual spraying.

II. ORIENTAL SORE

Synonyms. Tropical Sore; Bouton d'Orient; Delhi Boil; Cutaneous Leishmaniasis; Bouton de Biskra; Bouton de Bagdad; Aleppo Boil; Salek (Persia); Pendeh Sore (Southern Russia).

Definition.—A specific ulcerating granuloma of the skin, endemic within certain limited areas in many warm countries. It is caused by

Leishmania tropica. and is characterized by an initial papule which, after scaling and crusting over, generally breaks down into a slowly extending and very indolent ulcer. Healing after many months, it leaves a depressed scar. The sore is inoculable and, usually, protective against recurrence.

Geographical and seasonal distribution.—In the French Sudan the distribution of oriental sore is co-extensive with that of *P. papatasii*. De Cisneros and Gomez state that cutaneous leishmaniasis occurs in association with kala-azar in Province of Murcia, S. Spain. Italy (Abruzzi), Sicily, Crete, Cyprus, S. Spain. Asia Minor—Syria (Aleppo), Palestine (Jericho), Red Sea Province, Egypt (Zagazig and Minia), Eritrea, Iraq (Bagdad), Caucasus, Arabia, Persia. India (Lahore, Multan, Delhi, Dera-Ismail-Khan, etc.). Transcaspia, Turkestan (Tashkent and Bokhara), China, especially Hunan. Sudan, Nigeria, Darfur. In S. America it is often found, but not invariably, in association with naso-pharyngeal leishmaniasis, especially in Peru, Bolivia, Brazil, Guianas, Mexico (Map II).

In the tropics it is especially prevalent about the beginning of the cool season: in more temperate climates, towards the end of summer or early autumn. Years of prevalence may be succeeded by years of comparative rarity—possibly in harmony with altered sanitary conditions. In Delhi, for example, in 1864, from 40 to 70 per cent. of the resident Europeans were affected with the local sore; when certain sanitary improvements were made, the frequency of the disease was immediately materially

reduced.

Epidemiology and endemiology.—Although oriental sore may occur in countries where kala-azar is endemic, its distribution is as a rule quite distinct (see Map III). In India cutaneous leishmaniasis is confined to the west, whereas kala-azar is endemic on the east coast. In North Africa, oriental sore occurs north of latitude 35°, whereas kala-azar is found south of this line. In Persia and Iraq, where oriental sore is very common, kala-azar is rare, though cases have been reported by Reid from Shiraz in the former country. Central Asia is an exception for, according to Gerschenowitsch, they are found side by side, even in a single family, and both diseases have been seen in the same patient. Apparently also, recovery from cutaneous infection does not necessarily protect against subsequent infection by the kala-azar parasite. Oriental sore and kala-azar are found together in the Southern Sudan and also in Crete, where, according to Alder, their respective carriers, Phlebotomus sergenti and P. major, are both present.

In the endemic areas oriental sore appears to have a seasonal preference, making its appearance in the dry season between September and January, in cities like Aleppo and Bagdad, where the disease is very common. In Turkmenistan the maximal incidence is æstivo-autumnal. Children usually acquire it between 2 and 3 years of age, and natives rarely attain maturity without having had one or more sores. In fact, it may be said that nearly every woman in Bagdad bears on her face marks of the ravages of this disease and for centuries it has been the custom there to inoculate

children to prevent infection in later life.

Russian workers in Turkmenistan recognize two nosologically independent types, and that the non-ulcerating form is the most typical. Kojevnikov's types are: Leishmaniasis tarde exulcerans, "dry type," and Leishmaniasis culanea cito exulcerans, "moist type." The former is rural and derived from animal reservoirs (gerbilles): the latter, urban, from human sources.

Oriental sore occurs as a natural disease in dogs and cats. Canine kalaazar with cutaneous lesions has been found by Ho in Sian, China. The
organism has been demonstrated in cutaneous sores on the ears, lips, nose
and inner canthus of the eye of these animals in Teheran, Tashkent and
Iraq, where it is only seen during the winter months (Machattie, Mills and
Chadwick), and recently in South America and India; while Sinton has
shown that the leishmania sores occurring on the noses of dogs in India are
transmissible to man. Macaca monkeys are also easily inoculated.
Oriental sore has been found as a natural infection of the brown bear
and bullock in Turkmenistan, and on the nose of a horse by Bennett in
Kordofan. Natural infections in gerbilles (Rhombomys opimus) from
Turkmenistan are common. Other gerbilles, Meriones erythowns and
M. meridianus, and a "souslik," Spermophilopsis leptodactylus, have also
been found naturally infected. The vectors are Phlebotomus papatasii
and P. cancasicus. An allied form (L. myoxi) occurs in the dormouse.

Ætiology.—The causative parasite—Leishmania tropica—is found in numbers in the granulating tissue at the edge of the lesion and may be demonstrated in scrapings. They frequently occur in rosettes, often enclosed in macrophage cells or in leucocytes. L. tropica resembles L. donovani in its morphology and behaviour, and in culture on N.N.N. medium. To collect material for cultivation the surface of a non-ulcerating sore is painted with iodine, and the edge is then punctured with a fine glass pipette. Like L. donovani the parasites grow best in the water of condensation. In heavy infections the flagellate, or Leptomonas forms, appear within forty-eight hours. Then the parasites undergo identically the same changes as do L. donovani, but they are able to flourish in conjunction with contaminating micrococci which the leishmania of kala-azar cannot do.

Noguchi once made the interesting observation that the addition of immune serum from an experimentally inoculated rabbit causes the organisms to develop in clumps.

In Syrian hamsters, and occasionally in mice, L. tropica produces generalized visceral leishmaniasis. Monkeys, dogs, mice and Syrian hamsters are experimentally inoculable, whilst donkeys, goats and sheep are refractory. In man a certain degree of immunity is produced so that, as a rule, second attacks of oriental sore do not occur.

Senekji and Beattie inoculated a large number of volunteers in Bagdad with cultural forms of L. tropica, and reproduced sores in the great majority. Subsequent attempts at reinoculation were unsuccessful.

Transmission.—Wenyon (1911) first suggested the sandfly (Phlebotomus) as the vector in Bagdad and found that 6 per cent. of these

insects in Aleppo harboured a flagellate of the Leptomonas type in their intestines. Later, further confirmatory evidence was brought forward by the Sergents, Parrot, Donatien, and Béguet (1921), who produced oriental sores in Algiers after scarifying the skin and applying a saline suspension of crushed P. papatasii. The incubation period was two and a half months. These sandflies were caught in Biskra, where oriental sore is common, and transported 600 kilometres to Algiers, where the disease does not occur. Later still, Adler and Theodor repeated these experiments with a Herpetomonas which is a natural infection of P. papatasii. The development of L. tropica in the body of the sandfly resembles that already described for L. donovani. Adler and Theodor have strikingly confirmed this, and have produced infection of P. papatasii by feeding these sandflies through a membrane on emulsions of leishmania. Thus Adler and Ber (1941) produced 28 sores in five volunteers by the bites of infected sandflies.

The vector in North Africa and the Eastern Mediterranean is *P. papatasii*; in Crete, Iraq, India and Persia *P. sergenti*; and in Central Asia *P. caucasicus*. In Italy, according to Vanni, *P. perfiliewi* (mace-

donicus) is the chief carrier.

Pathology.—There is continuous progression of cellular changes, so much so that a section taken at any particular time cannot give a complete picture of the processes involved. In the early stages there is proliferation consisting almost entirely of reticular cells, which form a syncytium. This proliferation may be so dense as to interfere with nutrition of the epidermis, whilst the proliferating reticulum is packed with parasites. Later, there is an invasion of lymphocytes, plasma cells and large mononuclears, and occasionally giant cells, accompanied by a considerable diminution of parasites. It may, therefore, be regarded as part of a protective mechanism, albeit not a very successful one, because the lesion, though now containing relatively few parasites, may still persist for months. Gradually, the lesion is replaced by scar tissue. In some cases parasites are very scanty in all stages of the lesion and, in these, there is local infiltration of lymphocytes, plasma and giant cells. The histological, as well as the clinical picture may resemble lupus very closely.

Immunity.—A considerable degree of immunity is produced by repeated infection with oriental sore, which eventually becomes absolute—a fact which has been well recognized in Bagdad. On experimental grounds this was proved by Laveran, who found that repeated inoculation produced immunity in experimentally-infected dogs.

Incubation period.—The incubation period of oriental sore is variously stated in days, weeks, or months. That it may be a brief one, a few days or weeks, seems to be established by the appearance of the sore within a short time of arrival in endemic districts, or after inoculation. That it can be of much longer duration is equally certain. Manson saw an unquestionable oriental sore which did not appear until five months after the patient had been exposed to any possibility of infection. Wenyon inoculated himself with oriental sore in Aleppo, but it was not until six and a half months later that a leishmania-containing papule, subsequently developing into a sore, appeared at the site of inoculation. In some cases the incubation period appears to be as much

as fifteen months, or even longer. Sometimes eruption of the sores is accompanied by fever and other constitutional symptoms, and temperatures up to 103° F. have occasionally been noted.

Symptoms.—The local lesion in oriental sore commences as a minute itching papule which tends to expand somewhat as a shotty, congested infiltration of the dermis (Fig. 25). After a few days or weeks the surface of



Fig. 25.—Oriental sore. (After Wenyon. Photo: R. McKay, reproduced in "Journ. Lond. School Trop. Med.")

the papule becomes covered with fine, papery scales. At first these scales are dry and white; later they are moister, thicker, browner, and adherent. In this way, a crust is formed which, on falling off, or on being scratched off, uncovers a shallow ulcer. The sore now slowly extends, discharging a scanty ichorous material; this from time to time may become inspissated, and a crust forms, while the sore continues to spread underneath. The alcer extends by the erosion of its perpendicular, sharp-cut and jagged

edge, which is surrounded by an areola of congestion. Subsidiary sores may arise around the parent ulcer, into which they ultimately merge. These sores, usually about an inch in diameter, may come, in some instances, to occupy an area several inches across.

After a variable period, ranging from two or three to twelve or even more months, healing sets in. Granulation is slow and frequently interrupted. Often it commences at the centre, while the ulcer may be still extending at the edge; often it is effected under a crust. Ultimately, a depressed white or pinkish cicatrix is formed. Contraction of the scar may cause considerable and unsightly deformity. Thus, on the face,



Fig. 26.—Oriental sore on nose showing lymphatic soread to chin.

(By permission of Medical Department of the Navy.)

scar tissue may produce retraction of the external canthus (epiphora), deformity of the naso-labial folds or eversion of the angle of the mouth.

Oriental sore may be single or multiple. Two or three sores are not uncommon; in rare instances as many as one hundred and fifty have been counted on the same patient. They are mostly situated on uncovered parts—hands, feet, arms, legs and, especially in young children, on the face; rarely on the trunk; never on the palms, soles, or hairy scalp. Occasionally these ulcers may occur on the ears, tip of the nose ("Tapir nose") (Fig. 26), lower lip, and even on the tongue (Hawes, Panja, Dastidar, Trifilo), and three cases have been reported on the upper eyelids by Kamel in Cairo. These complications seem to be more frequent than had been supposed, and provide a link between the Old and New World leishmanissis. A small multiple diffuse form may

resemble diffuse papillomata: very rarely they occur on the buttocks or on the perineum. The Editor recorded a case in which a diffuse indurated

swelling close to the anus contained large numbers of L. tropica.

In a very few instances the initial papule does not proceed to ulceration, but persists as a scaling or scabbing, non-ulcerating, flattened plaque—just as sometimes happens in the primary sore of syphilis. Sometimes the ulcer is quite superficial, an erosion rather than an ulcer. Occasionally, from contamination with the organism of some other infectious acute inflammatory skin disease, the primary lesion may become complicated, and perhaps a source of serious danger. Otherwise, oriental sore is troublesome and unsightly, rather than painful or dangerous. When ulcerated, or secondarily infected, the neighbouring lymphatic glands in the area of the sore may be enlarged.

Associated subcutaneous nodules have frequently been described. Thus, Byron Evans (1988), in a case of extensive cutaneous leishmaniasis, found, around the arm lesions, five separate apple-jelly-like papules. Others were seen around similar lesions on the opposite arm or leg. In size they varied from 0.25 to 1 cm. in diameter; they were firm, discrete and freely movable and were not tender. On removal, they showed chronic inflammation with fibrosis, and Leishman-Donovan bodies, suggesting a chronic lymphatic infection and denoting the spread of the infection via the lymphatic route. Lymphatic nodules were described as early as 1847 by Poggioli and by Bonne (1901), and also, in association with South American leishmaniasis, by Darier, de Christmas, Escomel and Werner.

In Christopherson's case (1928) there were twenty-five vesicular lumps of varying sizes which contained leishmania, while the Editor found similar swellings on the dorsum of the hand and over the submental gland in his patient (Fig. 26). Gonzalez, Boggino and Rivarola described a similar case in 1987. A sharp bout of pyrexia (T. 108–104° F.) frequently precedes the appearance of the nodules.

Nodular or vertucose form.—A peculiar kind of dermal leishmaniasis, or parasitic granuloma, has been described by Ferguson and Richards in Egypt (Fig. 27). These lesions, which usually affect the lower extremities, resemble warty out-growths or papules; they may be solitary or multiple, and may be the result of auto-inoculation. They are best treated by excision.

Leishmaniasis recidiva.—The relapsing tuberculoid form, most frequent in Iraq and Anatolia, involving large areas of skin, especially of the face, is an allergic manifestation and therefore analogous to cutaneous tuberculides, closely resembling lupus vulgaris (Fig. 28).

It has been termed "metaleishmaniasis" by Marchionini. Some types

resemble erysipelas with "serviette" distribution on the face.

Allergic manifestations are common on the nose and sometimes there are blood-borne metastases resembling skin tuberculides. Chronic forms with dried and fissured scabs resemble tertiary syphilis.

Sometimes Leishman-Donovan bodies are very scanty in preparations, but they can usually be isolated by culture. Relapses occur after the original lesion heals and often take the form of nodules and papules, situated at the periphery of the scar and closely resemble "apple-jelly" nodules. Christopherson originally described them on the cheek, and also recognized a keloid form. Leishmaniasis recidiva is resistant to all forms of treatment except the Grenz rays.



Fig. 27.—Diffuse cutaneous leishmaniasis of the leg in an Egyptian. (Ferguson and Richards. By permission of Liverpool School of Trop. Med.)

Generalized non-ulcerating form (dermal leishmanoid).—Brahmachari described papillomatous nodules over the whole of the body, due to Leishman-Donovan bodies, which at first were thought to be tuberculoid leprosy (see p. 154), but all cases had previously been treated for kala-azar, and had apparently recovered after antimony injections.

Secondary infections.—Superadded staphylococcal or streptococcal infections are common. Secondary diphtheritic and streptothrical infections have been described.

Diagnosis.—On clinical grounds these sores have to be distinguished from the desert or veld sore (p. 666), tertiary syphilis, ulcus tropicum, lupus vulgaris, and blastomycosis. The distribution of the sores and the presence of the Leishman-Donovan body render the diagnosis not a difficult matter. The parasites are best demonstrated by sterilizing the skin at the edge of the ulcer, and running in a fine glass pipette through

a puncture made in the skin, to get beneath the ulcer, and obtain serum and tissue cells—but not blood—if possible free from bacterial contamination. This is a better method than scraping the surface of the ulcer with a blunt needle or with a fine knife. If parasites cannot be found, cultures

Fig. 28.—Cutaneous leishmaniasis in Egyptian girl. Lupus-like "apple-jelly" nodules. (Dr. H. K. Giffen, Assiut.)

should always be made. Additional help may be obtained by the leishmanin test: the intradernal injection of 0·1 ml. of a suspension of flagellates in culture (1,000,000 per ml.). A specific reaction is produced in active, as well as in healed, oriental sore lesions. Care must be taken to distinguish the Leishman-Donovan bodies from yeast cells, which are sometimes present in cutancous ulcers and may closely simulate them.

The aldehyde test is negative.

In leishmaniasis recidiva differential diagnosis has to be made from tuberculides of the hypoderm, including Bazin's disease and also from syphilis. Adler insists that the apple-jelly nodules so closely resemble lupus that cultures on NNN medium should

always be made to grow the parasites (Fig. 28).

TREATMENT

The treatment of oriental sores in general, especially in a temperate climate, does not, as a rule, entail any particular difficulties, for the reaction of the tissues to the particularly indolent ulceration depends to some extent upon the general nutrition and environmental conditions. When the patient is removed from the endemic area, the disease tends to disappear spontaneously in about one year.

(a) General measures.—When the sores are multiple, as they so often are, and when they are situated on the extremities, undoubtedly the best treatment is intravenous injections of antimony, especially the pentavalent compounds (p. 159). Foundin is the best trivalent compound given in 8-ml. doses on alternate days—three times weekly for 8-10 injections of the pentavalent. Neostibosan or Neostam are equally suitable and, when feasible, should be given intravenously in doses commencing with 0·1 grm. and increasing on alternate days to 0·3 and 0·4 grm. Much smaller total quantities (1-2 grm.) effect a cure than in kala-azar. For women and children, to whom injections cannot be given intravenously, the intramuscular route should be chosen (see p. 159). Solustibosan (p. 160), in only solution intramuscularly for ten injections twice weekly, is praised

by Marchionini in Turkey. Ball and Ryan found in 221 cases in American soldiers that neostam was most effective, intravenously, twice weekly, from 0.05 to 0.2 grm., with a total of 1.4 grm. The average time for cure was $14\frac{1}{2}$ weeks. Raymond and Cruickshank, in an account of an epidemic of these sores following the Quetta earthquake, found injection of trivalent antimony compounds (tartar emetic and foundin) combined with local scraping the most effective method. Pentavalent antimony preparations were less satisfactory under the conditions prevailing.

(b) Local measures.—Intravenous injections of antimony do not act so well for sores situated on the face—eyebrows, nose, cheeks, lips—and hands, which tend to be chronic, indurated, and subject to secondary infection.

Secondary infection is a most important element and in these cases no treatment is of any avail until the scabs have been removed and the sepsis cured by hot fomentations, eusol dressings, and nitrate of mercury ointment. Powdered sulphapyridine has proved beneficial (Akrawi), and penicillin has been used with good effect by Marchionini.

Ointments.—Various applications have been found useful on different occasions, e.g. *Cignolin* (a refined product of chrysophanic acid), in the following formula:

This paint should be applied to the sore with a camel-hair brush, care being taken not to overlap on to the surrounding skin, daily for 2-4 weeks, after the sores have been cleaned up with eusol dressings or boric fomentations. This treatment is especially applicable to sores on the face in children.

Other ointments which have been recommended are: *Pellidol* (Bayer), containing 2 per cent. diacetylamine-azol-toluol, *Desitin* (Klinke) (chlorine and cod-liver-oil salve), and *Orisol* ointment, which contains berberine sulphate. Good results have been reported from the local application of phosphorated oil, and also from finely-powdered permanganate of potash. The local application of vanadium in a preparation "Tarvan" is said to be a very active remedy (Pereira).

Injections into the base of the sores.—These methods of treatment probably act by causing a tissue reaction but, as a rule, injections are painful and, on account of the surrounding inflammation, cannot be used for sores on the face, especially near the eyes.

Good results are reported by Flarer (1938) and Marchionini (1948) by infiltrating the surrounding skin with solutions of atebrin in 15 per cent. solution, especially in the early stages. Berberian tested this treatment on six cases, artificially produced by cultures of *L. tropica*, with 1–2 ml. of 10 per cent. solution.

Treatment of indolent sores on the nose.—These require special mention as, on account of the induration of the surrounding tissues, they

are especially refractory and they do not appear to respond to the applications which are efficacious in other situations. After being cleansed, the bases should be scraped by a Volkmann's spoon and dilute nitrate of mercury ointment thoroughly rubbed in. Dry dressings and sulphonamide paste should subsequently be applied and pentavalent antimony injected intravenously.

X-ray therapy.—In Iraq it is stated that a single full-pastille dose of X-rays produces a cure within ten days in the majority of cases. The rays probably cause acceleration of the protective processes and infiltration of leucocytes into the base of the sores. An X-ray set capable of operating continuously at a voltage of 100–120 K.V. and 2–4 m.A. is suitable for the purpose. A filter of 0.5 mm. of aluminium is used at a focal skin distance (F.S.D.) of 23–25 cm. A total dosage of 450–1,000 "r" units is given, either in one dose or in two smaller doses at intervals of 10 days. (One crythema skin dose (E.S.D.=450 "r")=one pastille dose.)

Soft Grenz, or Bucky rays.—These are half-way between ultra-violet and X-rays. This form of treatment has been described by Dostrovsky and Sagher (1942). It has the special advantage that lesions overlying sensitive organs (eyelids, thyroid gland and genital organs) and the growing organs of children can be treated. Leishmaniasis recidiva has proved refractory to every form of therapy but this. The nodular and vertucose forms are especially amenable. The total dose employed for the latter is two exposures of 800 r with half value layer of 0-027 mm. aluminium, whilst for leishmaniasis recidiva the total is from 3,000-11,000 r with half value layer 90-02 mm. aluminium. The nodular type of lesion disappears in eight weeks, but with the relapsing form treatment may be spread over six to eight months.

Treatment by ionization.—This has also given satisfactory results. The ulcer is cleaned and covered with a pad consisting of sixteen layers of lint scaked in 2 per cent. zinc-sulphate solution; this is firmly applied under a zinc electrode by a bandage, and then connected with the positive pole of an electric current which is supplied by eighteen accumulators giving an average of 36-38 volts. A patient with a sore of an area of 1 in. in diameter can easily stand 10 m.A. as gauged by a resistance coil. The application is continued for twenty minutes, the pad being constantly moistened with zinc-sulphate solution.

Prophylaxis.—In the endemic areas insect repellents (see p. 101) should be used to protect the exposed parts against bites of Phlebotomus. Breeding places of this insect should be abolished. In Turkey, for instance, the local practice of plastering walls and sheds with cowdung which forms an ideal breeding medium for phlebotomus larvae should be prohibited. At night-time a fine-mesh netting, forty-five holes to the square inch, is necessary to exclude these insects (see Fig. 12). Dogs with suspicious-looking sores should not be permitted near dwellings. Prophylactic inoculation with cultures of Leishmania tropica, in the flagellate stage, has been practised in south-east Russia (Lawrow and Dubowskoj). Sores develop at the site of inoculation after an incubation period of two to six months. The immunity thus produced protects against further infection. Berberian states that, after inoculation of infective material, immunity takes 240 days to develop. This occurs when the papulc ulcerates and

commences to heal. Katzenellenbogen vaccinated 416 people in Palestine. In 45 a febrile allergic reaction developed. This inoculation campaign eventually produced favourable results.

III. LEISHMANIASIS AMERICANA

Synonyms. Espundia; Bubas Braziliana; Uta; Pian Bois; Forest Yaws (British Guiana); Bosch Yaws; Naso-pharyngeal Leish-

maniasis.

Geographical distribution and epidemiology.—South and Central America from Peninsula of Yucatan 21° N. latitude 30° S. in Argentine.

Prevalent in N. Argentine and Paraguay at 25° S. Brazil, São Paulo, Bahia, Rio de Janeiro (residential quarter), Peru between 5° and 25° South. British Honduras, Honduras, Martinique, Guatemala, Colombia, Costa Rica (Garcia), British, Dutch and French Guiana, Uruguay, Bolivia, Ecuador and Mexico (Campeche) (Map III).

Occasionally, somewhat similar clinical cases have been reported from the Sudan (Christopherson, Humphreys, Mayne and Kirk), Somaliland, Italy and Kenya (Piers, 1047).

1947), India and China.



Fig. 29.—Espundia from Ecuador. (Dr. L. A. Léon, Quito.)

Mutilations of the face, reminiscent of this disease, have been found in figures engraved on old Inca pottery.

It is prevalent in the northern part of Argentina and in Paraguay at 25° South. Altitude is a limiting factor. Most of the territory has an elevation of less than 2,000 feet. Heat and moisture are necessary for its existence. In the chicle (gum) forests of Yucatan the infection is contracted during the rainy season.

In highly endemic areas the majority of cases occur after six months residence, especially in the autumn. The prevalence of disease is definitely

related to the density of the sandflies which transmit it.

In Paraguay the disease has assumed epidemic characters, and a large proportion of the population in certain districts, and 70-80 per cent. of prospecting parties, have become affected, so that most drastic public measures have had to be taken to prevent its spread. It is usually seen in men working in the forests, especially gum-pickers. A similar disease

has been observed in the dog in the endemic centres, and it is possible that it occurs in the agouti (Dasyprocta). Kirk has produced espundia in a monkey, Cercopithecus ethiops, in the Sudan, infected experimentally with Sudanese kala-azar (1946). Amongst all the numerous animals thus infected this is the only one in which the oro-masal lesions of espundia have been observed. Pestana, Villela and co-workers working on the epidemiology of this disease in São Paulo, Brazil, concluded that intimate contact with wooded country is not always necessary. It is usually rural in distribution, but has been seen in some towns. Garcia thinks that in Colombia the dog is the reservoir of infection. The duration of the disease is from four months to four years. In the majority there are mixed mucosal and cutaneous lesions.

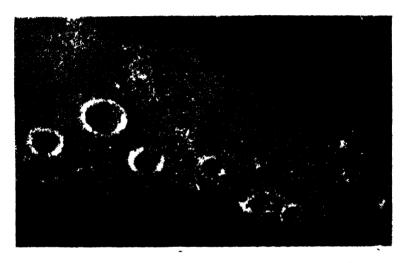


Fig. 30.—Punched-out ulcers in dermal leishmaniasis associated with Espundia in Ecuador. (Dr. L. A. Léon, Quito.)

Ætiology and symptoms.—The disease occurs at any age in either sex, in strangers as well as in the indigenous population. Sho Paulo seems to be an exception, as Villela says it is there nine times more common in men than in women. It begins as a sore on some mucous surface, of the chancrous form of the ordinary oriental-sore type. It heals in time, leaving a characteristic scar. After an interval of months or years, most intractable fungating and eroding ulcers (Fig. 29) break out on the tongue, and in the buccal and nasal cavities, destroying and obstructing them, and ultimately, if untreated, leading to death by exhaustion after years of suffering. The lymphatic glands are often involved, but the abdominal and thoracic organs are spared. Though affecting the mucous membranes in this characteristic manner in the endemic zones, ulcers, as in oriental sore, occur in other uncovered parts of the body (Fig. 30). They have been commonly noted as lupus-like lesions on the pinna of the ear in gumpickers (oreja de chieleros). For the state of São Paulo, Brumpt and

Pedroso record localization of sores as follows (in percentages): Leg 30, foot 12, forearm 12, head 11, hand 10, hip 4, elbow 4, trunk 3, nasal

mucosa 3, knee 2, buccal mucosa 2, neck 2, arm 1, pubes 1.

Leishman bodies are found, though not in great profusion, in scrapings and sections of the fungating ulcers, and present no morphological differences from L. tropica or L. donovani, but have been separated on serological grounds by Vianna as Leishmania braziliensis. The parasites can be cultivated in the same manner as L. tropica and on the same media, but Geiman showed that L. braziliensis, grown on the chorio-allantoic membrane of the chick embryo, shows much poorer infectivity than L. tropica. Giant cells and flagellated forms of the parasite have also been found in sections. It is believed that the original sore in this grave form of leishmaniasis develops at the site of the bite of a jungle insect, probably a sandfly—Phlebotomus—and the following species are suspected (Shattuck, 1935): P. squamipes (Dutch Guiana and Brazil): P. intermedius (Brazil and Argentina); P. migonei (Venezuela, Brazil, Paraguay and Argentina).

These sores infiltrate deeply into the tissues, and, besides grave destruction of the nose, lips, and tongue, they may be followed by secondary

infections, such as erysipelas and even gangrene.

Diagnosis is made upon the typical clinical appearances and the discovery of the parasite. Espundia has to be distinguished from ulcerating yaws (gangosa), lupus, leprosy and syphilis. In ulcerated lesions the crust should be removed and smears made from the underlying

seropurulent discharge.

The excision of a piece of granulation tissue and the expression of the contained serum on a slide often afford a more ready diagnosis. In five cases discovered in the Sudan, Humphreys and Mayne found the leishmania in material obtained by pinching the lobulated growths, but not by splenic puncture. The intradermal (leishmanin) test of Montenegro consists of an extract of flagellates (on culture) washed in physiological saline solution containing 0.4 per cent. phenol. This can be kept for long periods in the ice-chest. Gomes found it was moderately positive in 97.5 per cent. of South American cutaneous leishmaniasis.

The exact relationship of the mucosal leishmaniasis in the Sudan to espundia is not easy to determine. The South American disease has a specific course of evolution and occurs in epidemic form, which is not the case in the Sudan, where naso-pharyngeal leishmaniasis is relatively uncommon. In the nose the nasal septum and alæ nasi may be involved, whilst localized swellings occur on the lower lip. In almost every instance there, evidence of a concomitant visceral infection has been noted.

Treatment.—The general treatment is the same as for oriental sore; ten to twenty intravenous injections of antimony tartrate (20-30 gr.) or of the pentavalent compound, neostibosan, suffice for cure. The local ulcers on the lips and nose are cleaned up with fomentations, the cleansed surfaces anæsthetized with a mixture of cocaine, menthol, and carbolic acid, then sprinkled with finely powdered antimony tartrate and bound up with a

bandage. Subsequently the wounds are dressed with an ointment composed of zinc oxide, bismuth, and lanolin. From the buccal mucosa scabs must be removed with a solution of bicarbonate of soda, the surface anæsthetized with cocaine (1 per cent.) and sprayed with 1–2 per cent. antimony tartrate solution. Every four to eight days the tartrate is used in a saturated solution, the application being made on a pledget of cottonwool.

Mazza and others in northern Argentina had good results with intramuscular injections of *Fouadin* (or stibophen), a trivalent antimony compound, in doses varying from 0.5 to 5 ml. The treatment was continued for varying periods. Twenty to thirty injections are usually necessary and,

according to Schulemann, the results continue to be satisfactory.

Good results were obtained more recently by intramuscular injections of *Eparseno* (dioxy-diamido-arsenobenzol), prepared by Poulenc Frères, Paris. Injections of 0·12 to 0·25 grm. (I-2 ml.) are given and as many as 10-20 injections at intervals of two to three days are necessary. Others obtained success with similar injections of the double iodide of quinine and bismuth (0·15 grm. daily for one month). Atebrin (mepacrine hydrochloride) injections are advocated by Mazza and Cornejo in isolated sores: 5 ml. of a 10 per cent. solution is injected into the base of the sore and three tablets given by the mouth for seven days. Penicillin has also been used with success.

In assessing the relative value of the various treatments, it must be remembered that spontaneous cure appears to take place in about 7 per cent. of cases (Pessoa).

Subsection B.—FEVERS CAUSED BY BLOOD SPIROCHÆTES AND SPIRILLA

CHAPTER VII

RELAPSING FEVERS

Synonyms. Febris Recurrens; Spirillum Fever; Famine Fever; Tick Fever; Bilious Typhoid of Griesinger.

Definition.—A group of diseases, characterized by fever of sudden onset and, after several days (one to seven), rapid subsidence, which may relapse at intervals of from one to seven or more days for an indefinite number of times. They are caused by spirochætes, which are present in the blood during the fever and are transmitted by the body-louse (*Pediculus*) or by certain ticks (*Ornithodorus*).

Geographical distribution.—Louse-borne relaysing fever.—Europe.— Formerly in Britain, especially Ireland, also Norway, Denmark, Russia, Turkey, Bulgaria, Rumania, Yugoslavia. Africa.—Egypt, N. Africa, N. Equatorial Africa (South of Sahara), Gold Coast, Sudan, Kenya Highlands, China, Manchuria, and South Persia (Abadan), India—Central Province and N.W. Frontier. (A virulent epidemic, associated with jaundice, commenced in 1921 in N. Equatorial Africa, spreading across the Continent at 15° N. and continuous for over seven years. Thence it extended to Senegal and the Gold Coast to upper Guinea, French and British Nigeria, Wadai and West Egyptian Sudan. In clinical manifestations and virulence it resembled Yellow Fever.) African Tick Fever. -Senegal, Congo, East Africa, Uganda, Abyssinia and Madagascar, Transvaal (Kimberley), Cape Province (Græff-Reinet), Somaliland. W. American Tick-borne Relapsing Fever.—Colorado Valley, Texas and California. Central and S. American Relapsing Fever.—Panama, Venezuela and other S. American States. Other Tick-borne forms.-Spain, Morocco, Cyrenaica, Palestine, Cyprus, Turkmenistan, Syria and Persia.

Ætiology.—The various clinical forms of relapsing fever are caused by Spirochæta recurrentis, or organisms which are morphologically indistinguishable from it, but which may be biologically separable, such as S. duttoni and S. venezuelensis. (In American literature the generic term Borrelia is used for these spirochætes.)

Typically, the spirochete is a delicate spiral filament; its length varies from 8 to 15 μ , and its width from 0·2 μ to 0·3 μ . Each turn has an amplitude of 2 to 3 μ . The body of the parasite may have three, four, or six bends or turns; dividing forms appear to have more; in fact, the body of the spirochete undulates, it does not strictly form a spiral. Coles described the minute structure as

consisting of small granules in a containing tube and by the electron microscope flagella can be demonstrated. By the Romanowsky method the body of the parasite usually stains uniformly, with the exception of the extremities, which are pointed and take only a very faint tint. In fresh blood the spirochætes exhibit very active screw-like movement; some are longer than others, the long forms resulting from end-to-end attachment of two or more parasites. That this is the explanation of the long forms, which may measure from 16 to 100 μ , is shown by staining. In those measuring from 16 to 18 μ we find a pointed extremity at each end of the filament and a pale zone in the middle, the pale zone corresponding to the approximated lightly staining extremities. The still longer forms admit of a similar explanation. Although the normal habitat of the spirochætes is the liquor sanguinis, occasionally in fresh liquid blood preparations they are seen within the red blood-corpuscles, though this probably does not occur within the body.

Great variation is shown in morphology, but there is a consensus of opinion now that no constant distinctions exist between the organisms in the different clinical forms of the disease. For an explanation of the nomenclature the

reader is referred to p. 179.

Demonstration of the spirochæte.—The parasite occurs in the blood during the febrile stage of the disease only when the temperature is above 102° F., often disappearing some forty-eight hours before the crisis and being very scarce or entirely absent during the non-febrile intervals. In some forms and cases it is present in large numbers in every field of the microscope; in others it is so scanty that many fields have to be examined before a single specimen can be discovered. In thin films of fresh blood it can usually be recognized by the agitation its movements communicate to the adjacent corpuscles (Fig. 31). In dried and fixed films the stains in general use for malaria work suffice.

In children, especially, the spirochætes may often be found sparsely in the blood-stream during the apyretic periods.

Dark-ground illumination is admirably adapted for demonstrating the living parasites; a very strong illuminant, preferably a high-power electric-light—not always procurable in the tropics—is required. Occasionally, when very scarce in the blood-stream, as during a relapse, or in the clinical form met in North Africa, the organism may best be demonstrated by the "thick-film" method. Chung in China has demonstrated these spirochætes in the urine, but this appears to be quite exceptional.

Cultivation.—The successful cultivation of S. recurrentis and its sub-varieties was first obtained by Noguchi and others in sterile ascitic fluid containing citrated blood and a small amount of fresh kidney, incubated at 37° C. The greatest multiplication of the organisms takes place at the junction of the ascitic fluid and of the blood. Anaërobiosis is necessary and also the presence of coagulated albumin. The pH value of 7.2 is of great importance. The spirochætes reach their maximum development on the seventh to the ninth day, after which they begin to disintegrate. Subcultures retain their virulence for mice.

Chen in Peking obtained cultures on chick embryo. Blood containing S. recurrentis was inoculated beneath the chorio-allantoic membrane. A good growth of spirochætes was seen in the blood of the embryo reaching its maximum

on the fifth day.

Meleney found that the grey squirrel (Sciurotamias davidianus) and the striped chipmunk (Tamias asiaticus) can be experimentally infected with the Chinese strain. After splenectomy the virulence of the attacks in these animals was increased.

Different strains of relapsing-fever parasites (see Table II, p. 180).— The parasite, as originally described in Europe, is known as S. recurrentis. The Persian form of the disease (mianeh fever) is considered to be clinically distinct, and due to S. persica. The Central African disease. popularly known as tick fever (or carapata disease), is due to The South American form duttoni. is known as S. venezuelensis. In 1926 de Buen described a new variety, more resembling the Central African form. transmitted by ticks (Ornithodorus marocanus and O. erraticus) which live in the burrows of rats and porcupines, and the parasite has been named S.

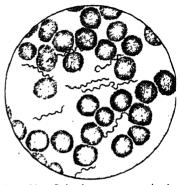


Fig. 31.—Spirochæta recurrentis in blood-film. × 500. (Microphotograph: Dr. John Bell.)

hispanica. In Turkmenistan a strain (S. persica or S. sogdianum) has been found to be transmitted by O. tholozani, which has proved to be the carrier there and also in Cyrenaica (Tobruk), Palestine, Cyprus, Persia and N.W. India.

Clark and Graham originally suggested that a tick-borne infection might occur in the Colorado Valley, Texas, and in California. Now it has been described by Wheeler, Herms and Meyer as due to S. turicata. It is transmitted by Ornithodorus hermsi, O. turicata, and possibly by O. parkeri

(see Appendix, p. 1012).

White mice and white rats are especially susceptible to these spirochetes, the former particularly so, the organisms appearing in the blood within twenty-four hours of inoculation and persisting to the third day. About this time they disappear for several days from the blood until the commencement of the first relapse, which may be followed by a second, third, or even a fourth, the number varying in individual mice; with each relapse the parasites reappear in the blood. The interval between the relapses is generally about seven days; occasionally it is only two, though it may be as many as ten. The actual number of organisms in the blood in the first is greater than in subsequent relapses, indicating the development of a partial immunity. Recovery in mice is the rule.

As a result of the consecutive passage of the spirochete through a long series of rats its virulence is augmented, so that the incubation period becomes reduced to 15–18 hours, and the persistence of the parasite in the blood is prolonged to 60 hours instead of, as originally, 48 hours; at

the same time they become far more abundant.

Some spirochates have a definite neurotropic tendency and, after subinoculation of S. duttoni in mice, a residual brain infection persists.

TABLE II SYNOPTICAL TABLE OF VARIOUS FORMS OF SPIROCHÆTA AND CLINICAL SYMPTOMS OF THE RELAPSING FEVERS THEY EVOKE IN MAN

Habitat and Strain.	COSMOPOLITAN: N. AND S. AMERICA. N. AND W. AFRICA.	TURKMENINIAN, PALES- TINE, PERSIA and NORTE- WEST INDIA.	SOUTH SPAIN AND MOROCCO.	AND CENTRAL AFRICA.	CALIFORNIA, TEXAS, IDAHO AND COLORADO.	CENTRAL (PANAMA) AND S. AMERICA (COLOM- DIA AND VENEZUELA).
	OHINA, EUROPE, INDIA Spirochæta recurrentis (obermeieri, novyt).		Spirochæla hispanica.	Spirochæla duttoni,	Spirochæta turicata.	Spirochæta venezuelensis (nvotropicalts).
Animals susceptible.	Small rodents, only after passage through mon- keys.	Monkeys (Macaca, Cercopithecus) rats, mice, field nive, guinea- pigs, hamsters, dogs, rabbits, badeers,	Guinea-pigs, desert foxes, Small rodents and many jackals, Morocean animals susceptible, and shrews,		Chipmunks (Tamius Sp.), armadilloes, squirrels (Sciarus douglasii)	Ry. Aurenean monkeys, marmosets (Edipomidas gordfrog), opossums gordfrog), armaululoes (Dasypus noremeneus).
Course in animals.	Mild.	Severe.	Severe,	Very severe.	Fairly severe.	Severe,
Subinoculations in animals.	Monkey to monkey, mouse to mouse. Per- sisting brain lesions.	Monkey to dog, rabbit and guinea-pig.	Guinea-pig to guinea- pig.	Monkey to monkey positive. Shrew-mice (*rocidura) and rats in Dakar. Brain infections.	White mouse to mouse , Marmoset to marmoset, and squirrel.	Marmoset to marmoset.
Course in man.	2-i relapses, Incubation period 2-10 days, Dura- tion of attack 5-6. Apyrexia 7-10.	Fairly severe attack, usually short, average 2-6 days. Relapses 1-14.	Apparently resembles the Central African form. Fairly severe with 4-f relapses of 3-4 days each.	Severe: 5-11 relapses, Resembles cosmopolitan Resembles Central Incubation period 7- form. African form. Many first attack 3. Aprevates 1-8. Compilical 1-8. Compilical forms are reviewed.	Resembles cosmopolitan form.	Resembles Central African form, Many cases bengn.
Natural transmitters.	Lice (Pediculus humanus).	Ticks (Ornithodorus Ticks tholoanni (papilitpes), erraiteus O. lahorensis) canus).	Ticks (Ornithodorus Ticks eraticus or 0. maro- moud tanus).	Ticks (Ornithodorus moubata, O. erraticus). Hereditary transmission.	Ticks (Ornithodorus hermst. O. turicata Texas), ? O parkeri.	Ornithodorus Tieks (Ornithodorus rene- O. turicata zuelense, O. turicata, O. O parkeri.
Serum reactions.	Immune serum not agglu- Large tinating S. dutioni. strains immuni	Large numbers of strains without cross-, immunity.	immune serum agglutinating S. currentis.	re- agglutinating S. re- currents.		Inmune serum not agglutinating 8, dustons,

N.B.-In all tick-borne infections transmission is hereditary; this does not occur in the louse-borne disease

In rats an acquired immunity may be produced which lasts for many months. As a rule, S. duttoni produces a far more severe disease in these animals than does S. recurrentis.

Rabbits and guinea-pigs are relatively refractory.

Dogs, rats and guinea-pigs are refractory to *S. venezuelensis*. Man and certain squirrel monkeys seem to be the chief reservoir of this spirochæte. Mice which have been made immune to *S. duttoni* can subsequently be infected by *S. venezuelensis*.

Pathology.—The spleen is usually large and soft, often shows multiple infarcts, necrotic nodules and fibrinous exudates, and may rupture spontaneously. Perisplenitis is common. Sterile abscesses may also form. In the 1945-46 epidemic in Egypt, El-Ramly found in 3,000 cases that 2.5 per cent. had infarctions of which 0.77 per cent. developed splenic abscess. Secondary infections of the abscess cavity may ensue. Sections of the spleen and liver show spirochetes within the endothelial cells and they are very abundant in necrotic lesions in the Malpighian bodies and constitute an important basis for differential diagnosis from yellow fever. Liver, kidneys, and heart show cloudy swelling of their cellular elements. The skin in fatal cases is usually jaundiced and there may be subcutaneous petechiæ. The bone-marrow is hyperæmic, shows great activity of the leucoblastic elements and there is generally a marked polymorphonuclear leucocytosis. Spirochætes are often phagocytosed by the leucocytes, but disappear rapidly after death. During the apyrexial periods an occasional spirochæte may be seen in the peripheral blood. Before a negative result can be claimed not less than 25 ml. must be injected into a susceptible animal which must be examined twice daily for at least ten days.

In Germany and Austria strains of relapsing fever spirochætes have been used for therapeutic inoculation in the same way as malaria. As the result of this study, it has been established that the spirochætes may be demonstrated in the liver, brain and cerebro-spinal fluid and that active infection may be produced by inoculation of susceptible animals with material obtained during the quiescent periods and even after apparent recovery.

Sagel showed that infection produced by the bite of a tick is much more virulent than that brought about by direct inoculation. Relapsing-fever spirochætes are remarkably neurotropic, and that in guinea-pigs the brain and cerebellum are still infective fourteen months after primary inoculation. A great deal of attention has recently been paid to this fixation in the brain of mice and birds. Similarly, Mathis and Durieux showed that strains of S. duttoni, originally isolated from shrew mice in Dakar, may persist in the brains of subinoculated mice up to 235 days.

Transmission.—There are two main forms of intermediary host which transmit relapsing fever, namely lice and ticks. It has been found possible to transmit S. duttoni through lice (Heisch) in the laboratory. A reservoir of infection of relapsing-fever spirochetes has been thought to exist, especially in Africa, in small rodents. Thus Nicolle and Anderson in Tunis suggested that the spirochete of these mammals, S. normandi, may be identical with S. duttoni (but Heisch has recently disproved this). This latter organism is virulent to rats and mice, but not pathogenic to

guinea pigs. The hispanica strain is equally virulent to mice, rats and

guinea pigs.

Russell in Accra (Gold Coast) and Boiron in Dakar found the pouched rat (Cricetomys gambianus) to be most susceptible to infection with S. duttoni, and suggested that the spirochete of the shrew mouse, S. crociduræ and that of the rat (R. alexandrinus), may be identical with S. duttoni. In Panama, Clark and Dunn found a wild squirrel monkey—Edipomidas geoffroyi—naturally infected with S. renezuelensis.

Epidemiology and endemiology.—The fever caused by S. recurrentis occurs, as a rule, at definite seasons of the year, depending upon the circumstances which favour the propagation of the intermediary host, the body-louse. In times of peace the poorer and indigenous class of the community is attacked. In Europe, for instance, relapsing fever has been a feature of famine, as has long been noted in Ireland, where it was once known as "famine fever." Widespread epidemics have occurred among the partially starved population of Central Russia. In war-time it is the scourge of armies in the field, and is commonly associated with epidemics of typhus, also a louse-borne disease; therefore the two infections may co-exist, as in the great Serbian epidemic of 1915. In Southern Europe and Northern Africa relapsing fever is a disease of the winter and spring months, at which time people are wont to envelop themselves in thicker clothes and to congregate together for warmth, thus facilitating transmission. Alarm was caused by the rapidly advancing and widespread epidemics of louse-borne relapsing fever which swept across Africa in 1921, starting from Upper Guinea. In two years the number of deaths caused in the French Sudan and the Niger was estimated at 80,000-100,000. In the upper Volta area it caused 20,000 deaths, and in 1926 in Darfur over 10,000. Generally speaking the louseborne disease is uncommon in Equatorial Africa, on account of the scantier clothing worn. In Dakar and certain parts of Senegal, however, the infection is tick-borne, and the spirochete is said to be identical with S. duttoni. In India it has been noted that at the advent of the hot weather, in April and May, the lice die off and the epidemics of relapsing fever come abruptly to an end.

The epidemiology of tick-borne relapsing fever differs from that of the louse-borne disease, as the former is associated with houses and localities which form a suitable environment for Ornithodorus, and is transmitted in a hereditary manner. In Central Africa it has been known for many years that the "rest-houses" on the main routes of travel are endemic centres of this fever, for the ticks live in the mud walls and roofs of the huts, and emerge at night-time to feed on man. There is therefore no seasonal incidence as in louse-borne relapsing fever. The same has been noted in the South American tick-borne form, except that a greater incidence is observed in the wet and rainy season, when native labourers and oil

prospectors are necessarily more confined to their quarters.

Evolution of the parasite in the intermediary host.—Philip Ross, Milne, Dutton and Todd showed definitely that S. duttoni is normally conveyed by O. moubata, and that it can be transmitted, not

only by the tick which has bitten the infected individual, but also by its progeny, even to the third generation (Koch). The spirochæte has been demonstrated within the eggs laid by infected ticks. From these eggs nymphs are produced in which the organism multiplies. Once fed on spirochæte-containing blood, ticks remain infective for one and a half years, and can convey relapsing fever by successive bites to at least ten monkeys (Fig. 32).

Wheeler, Herms and Meyer found a tick vector in California in Ornithodorus hermsi, which they collected from Lake Tahoe, Big Bear Lake, San Bernardino, Eldorado and Placer counties, at an elevation of 5,000-8,000 feet. These ticks were found naturally infected with the Californian strain, and produced infection in mice and monkeys. Chipmunks and squirrels, which abound there, seem to be the reservoirs of infection. Ticks

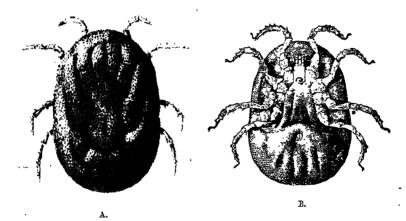


Fig. 32.—Ornithodorus moubata, Murray, \circ , \times 4. (After Smart). (By permission of the British Museum (Natural History).)

A. dorsal; B. ventral view.

fed on the Sierra Chickaree squirrel (*Sciurus douglasii*) infected a monkey. The most northerly focus is Mount Lassen at 5,800 feet. The bites of both male and female ticks in all instars are infective.

Development in the tick.—The cycle of development differs from that in the louse in that some spirochætes enter the solid organs of the tick, the cells of the gut, the Malpighian tubules, and the coxal and salivary glands. Some can even be found in the ovaries. They remain motile for several days after ingestion into the stomach, the duration depending on temperature. Complete development usually takes about ten days.

Transmission is effected by the saliva and secretion from the coxal glands. When the tick feeds on blood it makes a relatively large puncture in the skin and the saliva is delivered at the base of the mouth parts, so that presumably none enters the wound, but towards the end of feeding the tick evacuates the contents of its hind-gut, consisting partly of fæces and partly of nitrogenous waste from the Malpighian tubes. Fluid containing spirochætes is also excreted from the coxal glands through an

aperture at the base of the front legs. In O. moubata this occurs while the

tick is still feeding. (Fig. 32B.)

Transmission has been proved to be direct by bite from O. tholozani (Adler) and O. hermsi, as these ticks do not pass faces or coxal fluid when biting. If the puncture wound in an experimental animal be scraped and smears made spirochætes can readily be demonstrated. Relapsing fever spirochætes may survive within ticks for as long as $6\frac{1}{2}$ years.

Development in the louse.—According to Nicolle S. duttoni cannot normally be transmitted by lice; but Heisch (1949) in Kenya, has shown that batches of these insects collected from patients infected with S. duttoni, when emulsified, reproduced the disease when inoculated into rats

and mice.

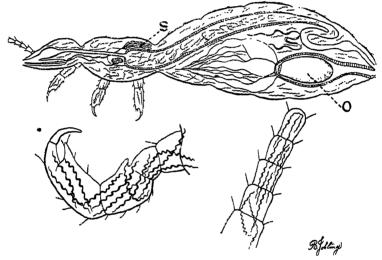


Fig. 33.—Spirochata recurrentis of relapsing fever and its development in the louse (Pediculus humanus). (C. M. Wenyon, Trans. Roy. Inst. of Great Brit.)

Diagram shows whole body invaded by spirochates. S. salivary glands; O. egg. Relow, spirochates in leg and antenna, which are easily broken off, so that fluid exading from the body infects the skin of the host.

The louse absorbs 1 mgm. of blood, which may contain large numbers of spirochetes (S. recurrentis). One day after ingestion they may be discovered in the insect's midgut (at 28° C.: 82° F.). At this stage some attach themselves to the epithelial cells lining the midgut; others invade the cells, while many die in the gut. By the end of the first day the spirochetes have disappeared, and there then follows a phase during which they can seldom be found in any part of the body. This was thought to be a "granular" phase, as in the tick, but the correctness of this question is difficult to decide as the tissues contain so many other kinds of granules. Adler and others now reject this theory and consider that the organisms persist as spirochetes, though difficult to find. After the eighth day (or even after a few hours—Chung and Feng, 1936) spirochetes appear in the blood of the louse, circulating through its body

cavity. They then increase rapidly and may be found in all parts of the body and limbs, but not in the lumen of the gut or within the salivary glands and ducts. These fully developed, or metacyclic spirochetes, persist in the body of the louse throughout its life, without causing any ill effects. Thus, a considerable proportion of lice taken from a relapsing fever patient may be found infested (Fig. 33).

When the spirochætes have reached the body cavity they have no natural means of egress and the louse can then bite man with impunity, but if a leg or antenna is injured or broken, the spirochætes escape and will enter any scratch or abrasion. Transmission probably normally takes place by man rupturing the louse with his nails and inoculating himself while scratching. As crushing kills the insect, one louse is capable of producing relapsing fever merely in one individual and, therefore, for this disease to assume epidemic proportions, lice must be extremely abundant.

Under optimum conditions 48 per cent. of lice become infected and remain so for 28 days. It is very unlikely that any spirochætes escape in louse excreta. There is no evidence of hereditary transmission in this insect. (The crab louse, *Phthirus pubis*, appears incapable of transmitting the spirochæte.)

Other methods of transmission.—The spirochætes have been proved capable of penetrating the mucous membrane and, if well rubbed in, the unbroken skin. Nurses and doctors treating relapsing-fever patients have been inoculated through the entry of infected blood into the conjunctival sac, and in pregnant women and experimental animals it has been proved that the organism can pass through the placenta to the fœtus. A particularly virulent infection is commonly found in China in heroin addicts, conveyed by dirty syringes, just like subtertian malaria (see p. 40).

Immunity.—Sabritschewsky, in 1896, showed that, when equal parts of spirochæte-infected blood or serum and normal serum are mixed, the spirochætes survive longer than when the infected blood is mixed with that of a patient who has recovered from relapsing fever. He accordingly concluded that the cause of the crisis in relapsing fever and of subsequent immunity was the development of some germicidal substance in the blood. He was the first to apply serum-therapy, and to obtain an anti-spirochætal serum by repeated innoculation of the horse with human spirochæte-containing blood.

Treated in vitro with hyper-immune serum, the spirochætes rapidly become unrecognizable aggregations of granules; this phenomenon may be manifest in a dilution of 1:2000.

Cunningham in 1925 showed that the spirochætes (S. recurrentis) which are found in the blood in the initial attack differ serologically from those which bring about the first relapse, and, on inoculation into animals, these strains maintain the same characteristics. Thus, if strain A be inoculated into an experimental squirrel, the initial attack will be of that serological strain, but in the subsequent relapse the strain will be B; but if the B strain be inoculated, the relapse will be A, and so on. There is thus an alternation of serological strains. It is probable that the antibodies produced in the blood-stream by one particular strain do not persist long enough to prevent relapses. The thrombocytobarin (Rieckenberg), or adhesion phenomenon, shows clearly that serological differences exist between spirochætes of the first attack and those of the second. On the other hand there are numerous immunological strains of tick-borne spirochætes, even in the same endemic area.

GENERAL SYMPTOMS COMMON TO ALL FORMS

I. EPIDEMIC COSMOPOLITAN LOUSE-BORNE TYPE (Spiroclueta recurrentis).—The course and character of the disease vary greatly in a single epidemic, and, further, the virulence of the more severe forms is much greater in some outbreaks than in others. The incubation period usually lasts from two to ten days. In some instances the attack develops promptly on exposure; but is never delayed beyond the fourteenth day. In those artificially inoculated symptoms show themselves in from two to six days.

The onset is generally abrupt, being characterized by chilliness or rigor, giddiness, epistaxis, vomiting, photophobia, intense headache, and pain in calves. In the young there may be convulsions. Temperature rises rapidly to 104° or 105° F., rarely to 108° (Chart 8). The pulse is rapid, 110 to 130. Should fever run high, there may be delirium. skin is dry, although, especially during the first day, occasional sweats may break out. A slight icteric tinting of the conjunctiva is usual and, not infrequently, jaundice is marked at the crisis. The spleon is invariably enlarged and tender. The tongue is coated and moist, except in severe cases, when it may become dry, brown, and painful on protrusion. The bowels, as a rule, are confined; abdominal pain may be considerable. and patients usually complain of pains in the muscles of the legs, especially the calves. Occasionally, herpes labialis is noted. There is quite commonly an erythematous rash in the initial fever, and later, rose-coloured spots on the trunk and limbs. Some authors describe petechiae. The rash has a peculiar distribution, being generally most marked round the meck. spreading in a semicircular fashion from the tips of the mastoid processes; thence it ranges symmetrically round the shoulders, down the sides of the chest and abdomen to the inner aspect of the thighs, and to the extensor and flexor aspects of the forearms. The individual petechie may be as large as a threepenny bit, and need to be carefully differentiated from the exanthemata of typhus and hamorrhagic smallpox. They are not easily detected on a dark skin.

Taft and Pike also describe a skin eruption resembling erythema multiforme which persists for one or two days. In biopsy made from the superficial layers spirochætes were demonstrated, even during the afebrile period. This is the first recorded instance of the discovery of these

spirochætes in the skin.

The primary remittent fever may last from five to seven days. At first the morning is usually lower than the evening temperature, but on or about the third day the evening temperature rarely rises above that of the morning. On the fourth, fifth, or sixth days there is again a rise of temperature, sometimes with delirium, ending in a crisis of profuse sweating and diarrhea. The temperature now falls rapidly to normal or subnormal, sometimes dropping in a few hours as much as 12° F.; in elderly or delicate patients there may be dangerous collapse.

The initial pyrexia, or first paroxysm, is followed by a first period of apyrexia during which the patient recovers so rapidly that after four or five days it may be difficult to keep him in hospital. But from seven to nine days after the crisis, that is about the fourteenth from the commencement of the attack, rigor again occurs, followed by a second attack of

fever—first relapse. This may be more severe than the initial paroxysm; usually it is milder, and seldom lasts so long. During it the secretion of urine is considerably increased; sweating also is profuse, and prostration marked. A polymorphonuclear leucocytosis of 15,000 to 30,000 is found during the pyrexial periods.

With the defervescence of the first relapse the patient enters on the second period of apyrexia, which usually coincides with convalescence (Chart 8). But in some patients a second relapse may occur, usually about the twenty-first day, counting from the onset of symptoms. This second relapse rarely lasts longer than three days, and is generally milder than the previous paroxysms. In rare instances three, four, five or even more relapses have been observed. Anomalous types of fever are common. Some temperature charts show an intermittent fever throughout, somewhat resembling that of phthisis. Cases with four relapses in a period of twenty-six days are met. Occasionally the apyrexial period may be of

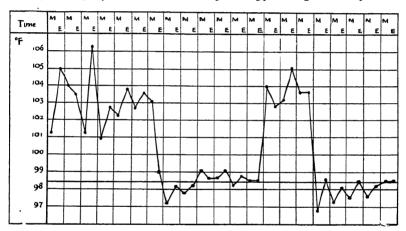


Chart 8.—Relapsing fever, cosmopolitan louse-borne type.

considerable length—seventeen days; in one case in particular, forty-two days. In some epidemics chronic diarrhœa, in others arthritis, are a feature.

Convalescence may be protracted, and complicated with such sequelæ as nephritis, ophthalmia, iritis, ædema of the eyelids, otorrhæa, polyarthritis, pneumonia, neuritis, parotitis, and adenitis. A mild type of encephalitis has been recorded (1943). In pregnant women abortion is the rule. In some cases attacks of abdominal pain resemble appendicitis. Spontaneous rupture of the spleen has been recorded. In one instance this organ weighed 315 grm.

BILIOUS TYPHOID FORM.—This is thought by some to be a distinct disease and, on account of the severity of its symptoms and rapidity of its course, especially on the West Coast of Africa, is apt to be mistaken for yellow fever. High fever, epistaxis, dyspnœa, intense jaundice, and enlargement of the spleen are noted. The jaundice is probably due to

toxic hepatitis. The liver is enlarged. The purpuric rash is a thrombocytopenic purpura and is associated with hemorrhages from the inucous membranes. Hæmorrhages into the skin and from the internal organs commonly occur; marked albuminuria is the rule.

Some cases become stuporose, with tympanites, hiccup, and severe diarrhæa. In Abyssinia intense dyspucea was a prominent feature. These severe forms are more generally seen in war-time, when in association with starvation and exhaustion, the disease assumes a more serious aspect.

II. Persian type (mianel disease).—This tickborne type is due to Spirochæta persica (sogdianum). It is found throughout Persia, and apparently also in Syria, Libya and Palestine. The symptoms may be said to be intermediate between those of the epidemic louse-borne and those of the Central African type, for, as compared with the former, the relapses are more numerous and of shorter duration, while the spirochætes

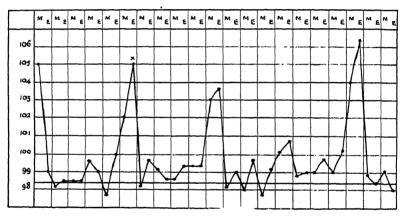


Chart 9.—Relapsing fever, Persian type. (Bellingham Smith.)
× Spirochates demonstrated in blood-film.

are very scarty in the peripheral blood, requiring a thick-drop method for their demonstration (Chart 9). The attack is generally moderately severe; the initial pyrexia shows marked morning intermissions, and lasts four to five days, when the temperature falls either by lysis or by crisis. Three, four, five or even more relapses are often noted, lasting sometimes only twenty-four hours, or, at a maximum, three days. The spleen is rarely enlarged, and icterus does not usually occur, but, according to Harold, in certain epidemics the disease may assume a more severe aspect. Jaundice and other complications may supervene, and the mortality may be high.

III. CENTRAL AFRICAN TYPE (carapata disease; tick fever; gorgoya, Somaliland) (Spirochueta duttoni).—The African tick-conveyed relapsing fever, caused by S. duttoni, although in type of fever resembling the epidemic European and Indian forms, differs in some important particulars. The initial fever is not usually so prolonged, generally terminating by crisis within three days. Diarrhea and dysenteric symptoms are not uncommon. The apyrexial intervals are of very irregular duration, being,

according to Philip Ross, sometimes as short as one day; sometimes as long as three weeks; and instead of only one or two relapses, as in ordinary relapsing fever, there may be as many as eleven; five or six relapses being the rule (Chart 10). The fever, though shorter, is as severe in the relapses as in the initial paroxysm, but the intervals tend to become longer, though there are exceptions. Sometimes the fever may assume a low chronic form, associated with a sharp cutting pain in the nape of the neck and vomiting. Iritis or iridocyclitis, uni- or bilateral, is a not uncommon complication or sequela. The liver and spleen are generally enlarged, and jaundice, bronchitis and pneumonia are frequent complications. The parasites, usually very scanty in peripheral blood, may be hard to find. There is a polymorphonuclear leucocytosis, as in the louse-borne type, and a slight microcytic anæmia.

Fulminating cases, in which the onset is very sudden, were observed nine times in a study of 1,500 cases during the East African campaign

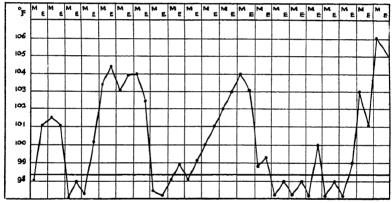


Chart 10.—Relapsing fever, Central African type. (Newham.)

(1914-1918) by J. K. Manson and Thornton. In these the spirochætes occur in enormous numbers; coma and death may ensue within twenty-four hours. Sometimes there is most intense icterus. These observers considered that death is brought about by impaction of masses of tangled spirochætes in the cerebral capillaries.

In natives of the endemic districts the disease, as generally observed, is not nearly so severe as in Europeans and strangers, being usually limited to a paroxysm or two of one or two days' duration. The mildness of these attacks is probably explained by a partial immunity conferred by previous infections. Charters has stated that the tick-borne relapsing fever in Somaliland is less severe than the louse-borne in Abyssinia.

Implication of the central nervous system, due to invasion by spirochetes, is not uncommon. A particularly distressing, but fortunately somewhat rare, complication is optic atrophy. Of this there are two forms—one which follows immediately upon the cessation of the fever, the other which gradually develops after the lapse of several months. Some

observers have described aphasia, facial paralysis, hemiplegia, and implication of the cranial nerves—such as the third, fourth, and sixth (resulting in ptosis and strabismus), the fifth (trigeminal neuralgia), the seventh (facial paralysis), and the eighth (deafness)—coming on suddenly during the course of the disease; others have recorded signs of meningitis. In these nervous complications spirochetes may sometimes be demonstrated in the cerebro-spinal fluid; as a rule, it contains an excess of lymphocytes and is under considerable pressure, necessitating lumbar puncture in order to relieve symptoms. Hawking in Tanganyika failed to find spirochetes on microscopic examination of cerebro-spinal fluid, though an intraperitoneal injection into mice produced infection. In patients infected with subtertian malaria a superimposed attack of relapsing fever may determine the onset of blackwater fever. Arthritis is not uncommon.

IV. Tick-borne Spanish type (Spirochæta hispanica).—The most complete study of the clinical aspects of this form of relapsing fever is by Más de Ayala (1931). The incubation period is apparently very short, 1–2 days, and the onset of the fever abrupt. It is ushered in by nausea, headache, chilliness, general malaise, a rise of temperature to 40° C. (104° F.) with congestion of the face and eyes, and dryness of the mouth and lips.

The initial pyrexia persists for 3-4 days and is associated with drowsiness, prostration, and generally with enlargement of the splcon. There is the usual rapid fall of temperature at the crisis, often associated with

collapse, and which responds to injections of adrenalin.

The periods of apyrexia and relapse correspond closely to those of the Central African form. After four attacks the disease apparently comes to an end spontaneously. The Spanish type of relapsing fever does not seem to be associated with secondary anemia, as in the other forms, though there is generally a leucocytosis of 14,000 to 26,000 per c.mm. during the attacks. Herpes labialis is common, and the urine often contains bile at the crisis. Enlargement of the cervical lymphatic glands is said to occur.

As in S. duttoni infections nerve complications have been noted. Facial paralysis has been seen in about 3 per cent. some six weeks after the last relapse, and iritis is noted in about the same proportion of cases. In the campaigns in the Libyan Desert Scott reported nerve-complications in 22 per cent. This spirochæte is neurotropic, so that meningitis, hemiparesis, facial palsy and ophthalmoplegia were recorded. The corebrospinal fluid was under pressure with lymphocytic pleceytosis, increased protein and globulin: spirochætes could rarely be demonstrated.

The prognosis is usually good. The immunity to this strain of spirochete

appears to last about a year.

V. TICK-BORNE, CALIFORNIAN, CENTRAL AND SOUTH AMERICAN TYPES (Spirocheta turicata and S. venezuelensis) present no special clinical features, but resemble in the main Central African tick-fever.

Ocular complications of relapsing fever.—These were studied by Hamilton (1943) in the Middle East. They are thought to be due to the presence of numerous spirochetes in the ocular blood vessels. Acute iridocyclitis merges into chronic cyclitis with persistent headache. Posterior synechiæ develop, which

may be broken down by midriatics. A gross vitreous exudate is marked. Despite cyclitis and vitreous changes, no choroiditis is observed. Prognosis for vision is good. These complications are specially marked in the louse-borne type. Optic atrophy appears to be confined to *S. duttoni* infections.

Mortality of relapsing fever.—The death-rate is usually below 6 per cent. In a serious form with jaundice, which has been noticed on the West Coast of Africa, the death-rate may exceed 50 per cent. In the feeble and old, death may ensue at the height of the first paroxysm, or from exhaustion as the result of relapses.

Diagnosis.—This fever is most usually confused with subtertian malaria, from which it may be at first indistinguishable on clinical grounds; it may also resemble leptospirosis, enteric, typhus, influenza, dengue, pneumonia, malignant smallpox, and even plague. In South America and West Africa it may be confused with yellow fever. Detection of the spirochætes with the microscope, or by animal inoculation, is the most reliable method of diagnosis, especially during the febrile paroxysms, and they are readily demonstrated with the dark-ground illumination. At an early stage the relapsing character of the fever is not available as an aid to diagnosis, but at a later period the history of a fever which had relapsed about fourteen days from the onset of the disease should be regarded as suggestive.

Wassermann reaction.—A strong pseudo-positive complement-deviation is obtainable, both during the pyrexial stage and in the apyrexial periods between the early relapses, in about 20 per cent. of cases. This apparently applies to all clinical types of the disease and therefore does not necessarily indicate a syphilitic infection. An efficient complement-fixation test has been elaborated by Wolstenholme and Gear (1948), employing as antigen a suspension of spirochætes (S. duttoni) grown on the choricallantoic membrane of the chick embryo. The test is useful for diagnosis in obscure cases as well as for assessing the effects of treatment.

Treatment.—Careful nursing and dieting are necessary, especially in the African type, and must be maintained after the crisis, when the patient may be ravenously hungry.

(1) Antibiotics.—Penicillin.—Based upon experimental studies on S. recurrentis in mice by Lourie and Collier (1944) and later by Eagle and Magnuson, the therapeutic efficacy of penicillin in the treatment of relapsing fever has been established. With full doses of 50,000 units at hourly intervals the spirochætes disappear from the blood of these animals within 24 hours. The two last named workers estimated the curative dose in man at 25 mega units.

Schuhardt and O'Bryan (1945) have shown that intracranial penicillin therapy cures brain infection in experimental relapsing fever in white rats.

Taft and Pike (1946), in two patients, gave penicillin in doses of 40,000 units every three hours for 60 doses—a total of 2,400,000 units—causing the fever to disappear within 72 hours. There were no relapses.

Greaves and colleagues treated 271 patients with louse-borne relapsing fever in Tunisia with penicillin. Total dosage was 480,000 units for adults and 360,000 for children. All showed a rapid clinical recovery. Ingraham and Lapenta (1946) injected 52 patients with the louse-borne type intramuscularly every three hours till a million units had been reached. No relapses occurred.

Muwazi (1946) treated 37 patients with "tick fever" (S. duttoni) in Uganda—a form which proved more resistant to penicillin. Eighteen received a total dosage of 9 mega I units of penicillin. The Egyptian strain of S. recurrentis has shown itself particularly amenable to penicillin.

Streptomycin.—Narain and Kalra have treated 18 patients in Kashmir with streptomycin daily in two divided doses at intervals of 3-4 hours for two consecutive days. Treatment began after the last paroxysm. The results were equally good in all cases. Streptomycin eured the two who did not respond to salvarsan. Levaditi and others have shown that streptomycin prevents residual brain infections in mice.

Aureomycin is also specific. Gilehrist gave aureomycin by the mouth in 0.5 grm. every six hours for six doses. In four the blood was free from spirochetes after one dose, in the other four after two. Apart from initial rise of temperature and rigors in a few cases the fall of pyrexia was dramatic. Aureomycin has an action upon spirochetes in mice.

Terranycin.—Berks and Goodwin (1950) working with S. duttoni in mice found it to be 40 times as potent as penicillin. Adler and colleagues (1952) with S. persica in rats found that a dose of 20 mgm. per kg. cleared the blood of spirochætes in two hours.

(2) Salvarsan,—Salvarsan and its allied preparations are specific when injected intravenously in doses of 0.3 grm. to 0.9 grm., according to the age of the patient and the severity of the case, the dosage being reckoned as 0.01 grm. for each kilogram of body-weight. After a short aggravation of symptoms a crisis takes place with disappearance of spirochetes from the blood and, in the vast majority of cases, recovery. Should relapse occur, a second injection may be given. Of the salvarsan (arsphenamine) compounds, undoubtedly novarsenobillon is the best; neosalvarsan, luargol, arsalyl, kharsivan, galyl (0.35 grm.) and salvarsan are useful in a descending order of merit, and recently sulphoxyl-salvarsan (Höchst) has given good results. The last mentioned, as also sulphostab (Boots), in doses ranging from 0-3 to 0.6 grm., have the additional advantage that they may be given by the intramuscular or deep subcutaneous routes. Evidence shows that salvarsan is most efficacious in the pre-critical period-that is, when the temperature is on the rise, directly the diagnosis has been made; relapses are apt to occur if it is given whilst the temperature is on the fall, or during the apprexial period; this is especially true of the Central African type, some cases of which appear to be resistant to salvarsan treatment. If it is not given in the first attack, it should be withheld until the first relapse, and then injected on the rise of temperature. It is generally agreed that salvarsan ought not to be injected when the crisis is imminent. A very grave reaction, due to the great destruction of the spirochetes and the liberation of their toxins, with corresponding aggravation of the symptoms, or, it may be, fatal collapse, is apt to ensue. On the other hand, the great majority of otherwise healthy patients recover from most forms of relapsing fever without any specific treatment, although convalescence may be prolonged. Albuminuria does not constitute a contra-indication to salvarsan treatment.

Hawking, who made a study of various methods, found the results of arsenical treatment difficult to evaluate. *Arsant*, a salvarsan compound, in which one or two arsenic atoms is replaced by antimony, has the same therapeutic value as neosalvarsan. The results of treatment of the tick-borne relapsing fever in Libya (1942), especially in Tobruk, with intravenous arsenicals, were not satisfactory. Cooper reported that relapses occurred in 40 out of 57 cases.

Arsenic-resistance is rapidly acquired by these spirochetes, so that Moretti and others who studied this problem found that arsenical compounds, which are efficacious in the earlier stages of relapsing fever, may be ineffectual if a prolonged

period (say of 100 days) is allowed to elapse between experimental infection with the spirochæte and the administration of the drug.

(3) Subsidiary methods.—The collapse and fall of blood-pressure with subnormal temperature which follow the crisis have to be counteracted by strychnine, brandy, intrarectal douches of hot salines, and by injections of adrenalin and ephedrine. Vitamin K is indicated for the hæmorrhages.

Prophylaxis (see Table III).—In the louse-conveyed forms of relapsing fever prophylactic measures are necessarily aimed at the destruction of lice and their eggs by all measures known to sanitary science—often a matter of very considerable difficulty when dealing with large groups of native porters or labourers, especially during the rainy season. Disinfestation is performed by superheated steam in a portable Thresh's disinfector, or in specially constructed cars in a disinfecting train, the superheated steam being supplied by the locomotive. Garnham has found that DDT mixed with powdered kaolin constitutes the best method of disinfecting native clothing. (For recent measures of louse destruction, see p. 865.)

In the African form, prophylactic measures are much more difficult, and necessitate intimate knowledge of the habits of ornithodorus, which does not live on the body of its victim, but emerges at night-time from the native houses to feed on blood. It is also found on the veld, living in the burrows of the wart-hog, but as a rule it is only met in numbers in the vicinity of old camping sites (see p. 1012). The tick itself is very difficult to destroy, but can be controlled by gammexane (B.H.C.).

The following rules are necessary:

1. Avoidance of native houses, most of all at night-time—especially those situated on much-frequented routes. Bedsteads of

TADDE III					
	Lpidemic Louse Relapsing Fever	African Tick Fever	Other Tick Fevers		
Vector	Pediculus humanus.	Ornithodorus moubata.	Other species of Or- nithodorus.		
Haunts	Human body and clothes.	Floors, cracks, court- yards.	Rodent burrows.		
Transmission	Crushed lice: not hereditary.	Coxal fluid, fæces; hereditary.	In some cases doubt- ful; hereditary.		
Reservoirs	Man.	Probably man only. Maybe mice or shrews.	Rodents, squirrels and other animals.		
Biology	Pediculus feeds only on man; short- lived.		Species of ornitho- dorus feed on animals; occasionally on man; live for months or years.		
Disease type	Epidemic.	House disease.	Sporadic.		
Control	Louse control, D.D.T.	Destruction of buildings. Concrete dwellings. Gammexane. Pyrethrum in oil.	Difficult; based on habits of normal hosts or ticks. Gammexane.		

TABLE III

native manufacture should also not be used. Camps should be

placed as far distant as possible from native villages.

2. Avoidance of much-frequented ground for camping sites; ornithodorus can exist without food for years. Sleeping on the ground should not be practised unless absolutely necessary, and only when well protected by a mosquito-net. A night-light is recommended to scare away the ticks. Blankets should be carefully inspected before retiring to rest.

Native huts should be so constructed that a space of 8-10 in. intervenes between the walls and the ground. Mud and rubble buildings are inadvisable; floors should be raised, and made of cement. A deep trench dug round a building and filled with wood-ash has been found effective in excluding ticks. A solution of pyrethrum in white oil (0.13 per cent.) has been found an efficient insecticide for O. moubata, applied either directly to the ticks or to floors or bedsteads (see Chapter LII for effect of DDT and Gammexane).

Children especially act as a reservoir of the spirocheetes and the ticks

feed upon them.

Prophylactic inoculation.—Attempts to immunize the inhabitants of an infected district have been undertaken by Russian workers with a vaccine composed of a mixture of cultures of the original and relapse strains of S. recurrentis, incubated at 37° C. for three days and subsequently kept at room temperature for 14–16 days until they had lost their virulence. Each man received 1·0, 1·5, and 2·0 ml. at three days' interval. A week after the last injection the blood was found to contain spirochætolysins against both original and relapse strains. The results showed that it was possible to produce immunity by inoculation of dead spirochætes.

For a description of the ticks and their habits, see p. 1011.

CHAPTER VIII

LEPTOSPIROSIS

In has become possible, through the discovery that certain delicate spirochætes (leptospires) are present in the bloodstream and in various viscera, to group together certain fevers which have certain clinical features in common. Under the heading of Leptospirosis are included infectious jaundice, canicola fever, seven-day fever, and possibly other certain less well-defined types.

WEIL'S DISEASE

Synonyms. Icterus Gravis; Spirochætosis Icterohæmorrhagica Mediterranean Yellow Fever; Griesinger's Disease; Odan-eki (Japanese).

Definition.—A fever, especially found in sewer workers, caused by Leptospira icterohæmorrhagiæ and its varieties, associated, though not invariably, with jaundice and enlargement of the liver. The natural reservoir of infection is usually the rat (Rattus rattus, R. norvegicus) and field mice (Microtus montebelloi). Since the original discovery by Inada and Ido (1915) some 40 separate antigenic types have been differentiated and are known as leptospires. A survey of studies in Indonesia was given by Walch-Sordrager (1939).

Geographical distribution.—Formerly thought to be especially prevalent in Japan, but has now been recorded from most countries in Europe. It occurred extensively in the 1914–1918 war in Gallipoli, Salonika, Egypt and France, North African Coast, and Mediterranean area in general. It appears to be specially common in Holland and Germany. In West Africa it is endemic in the Congo (near Lake Kivu), French Equatorial Africa, Sudan, Abyssinia. In the Western Hemisphere it has been reported from the United States, Peru, Brazil and Argentine, and British Guiana. Epidemics have been reported in the Andaman Islands, Indonesia and Malaya. There are no records from the Sudan and South Africa.

The disease in the tropics is said to be specially virulent, though further researches on this point, as well as on its distribution in hot countries, are necessary. In Europe it is said to be commoner in summer-time in Holland, where Schüffner observed 451 cases in ten years; it is specially prevalent in the south and in Rotterdam. The Editor, in 1922, recorded a case from the London docks; others have been observed in Scottish coal-mines (Buchanan), and in Aberdeen. In 1934 it was shown by Fairley that Weil's disease is by no means uncommon in the sewer workers of London, and this was soon confirmed in Liverpool and other cities. It is also not infrequent in canal workers. In 1944 an outbreak was recorded amongst British troops in Normandy which persisted from the middle of July to the end of September.

Epidemiology and endemiology.—In Japan the disease has a definite seasonal incidence, occurring, as a rule, most frequently in the months of September to November. The organism is found as a harmless commensal in the kidneys of wild rats and mice, and is excreted in their urine. The disease is therefore usually endemic among farmers and miners who are exposed to wet soil and water conditions, such as prevailed in trench warfare and caused outbreaks in 1916 and 1917 in France. In the Andamans, leptospirosis is prevalent during the South-West Monsoon, and confined to adult males engaged in outdoor occupations.

In some cases water appears to be the source of infection, as first shown by the Editor in 1922. Epidemics have been recorded among soldiers in Italy and in Germany after bathing in certain river pools. Since then several other British infections from the same sources have been reported. It is now known that spirochaetes of the leptospira type are widely distributed in water, some of which have been proved pathogenic to guinea-pigs (Zuelzer).

In Holland Schüffner showed that the highest incidence is amongst those whose occupation brings them near canals, and especially those who

have fallen in by accident.

Schüffner demonstrated that the non-pathogenic L. biflexa (Zuelzer) occurs in any kind of water, but that pathogenic L. icterohamorrhagiae can be demonstrated by immersing experimental guinea-pigs in suspected pools.

Slime fever (L. grippotyphosa) is an abortive form of Weil's disease prevalent in Germany, where it is often acquired during bathing. No less than 700 cases were reported in July, 1926. The attack begins with a rigor and a rise of temperature to 104° F. "Field fever", or Maladie des porchers in Savoy, in pigs and man, is due to L. pomona.

Schüffner and Uhlenhuth described outbreaks of infection with L. grippotyphosa in Holland and Germany, and the part played by voles (Microtus arvalis). Children are mainly infected during play in the fields, where they collect these rodents and are frequently bitten by them. In Switzerland the disease is known as "swine meningitis." It has now been established that it is primarily a field-mouse infection similar to that of rats, but in the former the leptospira exists as a temporary and evanescent infection. In the Kivu district of the Congo van Riel has found a local rodent (Arvicanthus abyssinicus) infected with L. grippotyphosa and L. bataviæ.

Annual outbreaks of leptospirosis of great severity were reported in 1938 and 1934 in Queensland. These occurred among sugar-cane cutters and farmers, especially after prolonged rainfall, the infection having entered through scarifications of arms and legs. A native species of rat (Rattus culmorum) appeared to be the carrier of the infection. In 1934, Davidson, Campbell, Rae and Smith described an epidemic of nineteen cases in Aberdeen, chiefly among fish workers. The patients were handling fish in rat-infested premises, the floors of which became covered with slime and offal. The hands are traumatized in doing this work, so that the infection can enter. Depilated guinea-pigs were easily infected with water obtained from this source. In the United States an outbreak in fish workers was reported by Glotzer (1988). Leptospirosis has, therefore, become an "occupational disease."

The disease occurs in dogs, especially hounds, in which it is known as "the yellows," and has been recognized in the fox, especially the silver variety, and in leopards, especially when fed on rats. Stuart (1946) and others have shown that healthy dogs harbour both *L. icterohæmorrhagiæ* and *L. canicola*. Broom and MacIntyre (1948) have proved that in 27 per cent. of healthy dogs the serum agglutinates leptospires, and that the great majority of the positive results are due to *L. canicola*. Canine epidemic gastritis and canine typhus ("Stuttgart disease") is identical with it. Baber and Stuart (1946) and Minkenhof (1948) have identified 49 human infections with this variety in Holland from 1933–1947. Others have been recorded in Austria, Denmark, California, Norway and in England where an increasing number of cases have been identified by Broom (1948) and colleagues. "Canicola fever" has therefore become increasingly common in Britain.

Ætiology.—L. icterohæmorrhagiæ is found in the blood, urine, cerebrospinal fluid and sputum. It is a spiral filament with wide flexures, the





Fig. 34.—Microphotograph of Leptospira icterohæmorrhagiæ from kidney of rat. × 3,000. (Dr. A. C. Coles.)

individual spirals being in close apposition (Fig. 34). The largest forms attain a size of 20 μ by 0.25 μ , the average length being 6-12 μ .

It is now generally agreed that the organism is identical with L. icteroides, the organism described by Noguchi in yellow fever.

The organism may be demonstrated by the dark-ground illumination, but is so extremely active that its movements can only be seen with difficulty. According to Fletcher, it is most readily demonstrated in blood-films by Fontana's method. Although easily demonstrated in guinea-pigs, it can be found in human blood only after prolonged search. In microscopic sections of infected organs the leptospiræ show up well with Levaditi's method of silver-nitrate impregnation.

The organisms exhibit rapid movements; when free, one end is extended and straight the other semicircularly hooked, so that they progress in the direction of the straight portion and appear to be propelled from the rear by the rotating hook.

This parasite was cultivated by Noguchi on solid media such as blood-agar or gelatin. According to Fletcher, it grows readily on agar impregnated with immune serum, but is agglutinated thereby in a peculiar manner. The culture medium used by Dutch workers consists of tap-water 1,500 ml., Witte's peptone 0-15 grm., Ringer's solution 300 ml., and Sorensen's solution of pH 7-2. The final reaction of this peptone medium should be between pH 6-8 and pH 7-2.

Three millilitres are placed in a small tube and sterilized, and 3 ml. of rabbit's serum is added. The tubes are then heated to 56° C. for thirty minutes and incubated at 37° C. overnight: thereafter at 25–30° C. Leptospiræ are seen by the dark-ground illumination on the fifth or sixth day. Stefanopoulo, Morrow and other workers have cultivated L. icterohamorrhagiæ on the chorioallantoic membrane of the chick embryo. Leptospiræ can survive for several days in whole clotted blood.

According to Fletcher and Broom, there are distinct serological races of L. icterohæmorrhagiæ, the Andaman, Indian, and Sumatran strains being distinguishable from those found in Europe and elsewhere. A score or more are

found in Indonesia and only two in Britain.

Schüffner distinguished the dog strain, *L. canicola*, which is found in Holland. *L. grippotyphosa* (Tarassof) is the name applied to the agent of "swamp fever," or "maladie de la vase," in Eastern Europe (Korthoff); it is characterized by severe jaundice and is closely allied to *L. bovis* and *L. pomona* which cause severe disease in cattle, pigs and goats in the tropics.

Fletcher and his staff in Kuala Lumpur found that the organisms isolated from 26 patients could be separated serologically into six groups, whilst Baermann and Smits in Sumatra have studied nearly 400 cases. The symptoms of this form are mild and much more closely resemble benign forms of relapsing fever.

The febrile periods last from 2-4 days.

Strains of organism isolated in Queensland by Clayton and Derrick differ from those of European origin and more closely resemble Sumatran types. They were provisionally named L. australis A and B; the latter is closely related to L. canicola.

There is some divergence of opinion on the advisability of regarding scrological races of leptospira as distinct species. Methods of differentiation, such as the Rieckenberg reaction, are considered by some to be too delicate and uncertain. Antigenic types are now separated by scrological methods and are referred to as scrotypes and assembled into scrogroups. According to Broom organisms from Malaya can be identified as L. bangkinang, L. bataviæ, L. hyos, L. medanensis, L. pyrogenes (see p. 206) and L. rachmat.

The common natural reservoir of the leptospira appears to be the rat, in which it occurs in the fæces, urine, and kidneys, though it has not yet been demonstrated in the blood. The disease is believed to have been originally epizootic in rats, but these animals have now become tolerant. The leptospira has been demonstrated in 32.4 per cent. of wild rats in Japan, in 56 per cent. in Holland (Schüffner), less frequently in France, Tunis and Algiers, and in 4 per cent. of sewer-rats in London. In the United States the proportion varies from 4 to 33 per cent. L. icterohæmorrhagiæ has been demonstrated by Buchanan in the zooglea-like "roof-slime," which constitutes a source of infection in certain coal-mines in Scotland. It has also been found in the green slime of sewers in London by J. M. Alston. Probably in this case the portal of entry is through skin abrasions, and guinea-pigs have been infected by rubbing cultures, slime or suspected water through the skin. Water again may be a source of infection, especially when it comes into contact with the bronchial epithelium, as by diving and swimming the "crawl stroke" (Schüffner). In Sumatra it is thought that native dogs may constitute a reservoir, as Kouwenaar and Wolff found 6 per cent. of dogs in Medan to be carriers, and the organisms were proved to be present in the kidney tissues. Occasionally, human cases of infection by L. canicola have been found in Holland and in England too (Lawrent, Broom, and colleagues). The dogs may be quite normal or present symptoms. Human cases from the bites of infected rats have also been reported.

Guinea-pigs are very susceptible to experimental infection, and so also, but to a lesser degree, are dogs and puppies, rabbits and monkeys. To produce the disease in these animals, 3–5 ml. of the patient's blood is required, and should be injected intraperitoneally; the animal dies of intense jaundice about the tenth day.

Pathology.—The liver is invariably increased in size, and may weigh 100-150 oz. The gall-bladder is generally half-filled with brown or greenishbrown bile. The various microscopic lesions are reducible to three main types. In the first there is little destruction of the parenchyma or intercellular tissue; the second is characterized by extreme cellular degeneration; in the third there is a localized destruction of glandular tissue. The fatty degeneration of the liver in Weil's disease is moderate and not so advanced as that seen in acute yellow atrophy. The leptospiræ can be demonstrated among the cells in large numbers by Levaditi's method. There is remarkable similarity between the pathology of this disease in man and in infected guinea-pigs. In the liver the cells appear to be killed individually, not in bulk. The spleen may be enlarged and the glandular substance soft and diffluent (about 12 oz.). A generalized enlargement of the lymphatic glands, especially at the hilum of the liver, with hyperplasia and multiplication of the mononuclear cells, has been noted. Hæmorrhages occur in the kidneys, mostly in the intertubular tissues; later in the disease the microscopic picture may resemble that of early interstitial nephritis, and leptospires may be demonstrated in great profusion. cells of the convoluted tubules are specially attacked. The renal lesions infected with L. canicola have been studied by McIntyre and Montgomery, who have shown that the intense cellular infiltration, limited to the boundary zone, implies the operation of the renal-shunt mechanism of Trueta. The picture is similar to that found in blackwater fever and the crush syndrome. Blood escapes into the glomerular capsule and down the lumen of the tubule. A characteristic type of non-inflammatory degeneration affecting small groups of voluntary muscle, particularly the gastrocnemius, has been described. The cytoplasm loses its cellular detail and strictions disappear. There is said to be a reduction in the hæmoglobin and polymorphonuclear leucocytosis of 10,000 or more. There is also a reduction in the number of blood-platelets to 10,000 per c.mm. (normally 300,000). The coagulation-time of the blood is increased to twenty minutes.

Inoculated guinea-pigs and pupples show marked tendency to bleed; hæmorrhages into the lung impart a characteristic appearance, the so-called "butterfly lung," or "butterfly patches."

Symptoms.—The clinical symptoms can be divided into the first, or febrile, the second, or icteric, and the third, or convalescent stage. Sometimes the curious phenomenon of "after-fever" is observed. The incubation period in man, as well as in experimental animals, is from six to eight, seldom as long as thirteen days. The onset is acute, with rigors, vomiting, headache, diarrhœa, and abdominal pains, which may simulate acute appendicitis. A few hours later, fever ensues, with thirst and very severe general aching of the limbs. There is intense injection of the eyes, which may constitute the earliest and most striking feature and is almost pathognomonic. A distinct network of vessels is seen on the

cornea and sclerotics. This reaction is believed to be due to primary invasion of the conjunctiva by leptospiræ. There is also a red plush-like injection of the soft palate, and often herpes labialis, which may be hæmorrhagic. The intense prostration, the almost agonizing muscular pains and aching of the bones, with hyperesthesia of the calf muscles. as if the muscles were being cut through with a knife, constitute the most distressing features of the illness. The muscles themselves are very tender. The pyrexia is irregular, between 103° and 105° F., falling by lysis in severe cases about the tenth or eleventh day. There is usually a secondary terminal rise of temperature lasting three to nine days, which is associated with excretion of leptospires from the urinary tubules. Convalescence is established in the third week, but there is sometimes a short temporary recrudescence of fever (" after fever "), which is thought to be an allergic phenomenon. Jaundice, which occurs in 50 per cent. of cases, is noted in from forty-eight to seventy-two hours from the onset and may be ushered in by hæmorrhages into conjunctivæ or skin, or even from mucous surfaces. Both icterus and hæmorrhage are ascribed to interference with prothrombin production in the liver. The skin is lemon- or orange-coloured, rarely greenish, pruritus being very frequent. The icterus is probably dependent on disorganization of function of hepatic cells, and is also due in part to hamolytic icterus following destruction and phagocytosis of red blood corpuscles. The Van den Bergh reaction is therefore almost always biphasic. The jaundice becomes progressively deeper until the ninth or tenth day, but afterwards fades with great rapidity. From the fourth day onwards there may be rashes, morbilliform, crythematous or papular, over the loins, sides of the abdomen and below the scapulæ, symmetrically distributed. A purpuric rash betokens a bad prognosis. Large black hæmorrhagic spots are sometimes seen.

The urine is highly coloured, nearly always containing albumin (which may be fleeting) and bile, and sometimes casts and red blood-corpuscles. The amount is reduced, and the albumin content may be considerable, and usually persists for seven to ten days, after which a trace only may be found. Bile pigments have been noted in the urine in patients without overt jaundice. The blood-urea is usually raised before the tenth day of the disease, and a secondary rise occurs during the secondary fever. The leptospiræ may be demonstrated in the urine from the tenth day to the twenty-fifth, and may persist as long as 63 days. They can seldom

be recovered from the blood after the twelfth day.

Prostration may be extreme. Constipation is the rule, but the fæces contain abundant bile. The pulse is slow in the later stages, and the blood-pressure low. A polymorphonuclear leucocytosis, of 10,000 per c.mm. or over, is present with an Arneth "shift to the left"; later there is an increase in lymphocytes. A high blood-urea of 200-800 mgm. per 100 ml. of blood is usually found, but is not necessarily serious. Gardner and Wylie emphasize that renal lesions develop early and that too much emphasis is liable to be laid on the hepatic aspect. The liver may be enlarged, but splenomegaly is quite exceptional; the gall-bladder is distended and tender; the lymphatic glands, especially the inguinal and axillary, are often palpable and tender.

The third or convalescent stage begins on the thirteenth or fourteenth day with rapid subsidence of the icterus. The patient remains weak, anæmic and emaciated. During convalescence guinea-pigs can still be infected by injection of urinary sediment.

Mild form.—After three or four days, in mild cases, the fever subsides by lysis. Slight or even severe febrile relapses are often seen at the beginning of the third week. Davidson (1987) and Sladen (1989) called attention to "subclinical" forms in those exposed to infection. Mild or

anicteric infections usually escape diagnosis.

Varieties.—Typhoidal, uræmic, and meningeal forms—all of great gravity—have been described. In the typhoidal type there may be black vomit, delirium, and muscular twitchings. Insommia is invariable. In the meningeal type the cerebro-spinal fluid is under pressure, and contains excess of albumin and leptospires in large numbers. Three cases were recorded in British troops in Normandy by Bulmer in 1944, but only one of these had abnormal cerebro-spinal fluid. Murgatroyd has described a peculiarly chronic meningeal form in which the leptospires were recovered from the cerebro-spinal fluid six months, and from the urine eight months, after the onset of the illness. Mollaret and Erber have found that forms of leptospiral meningitis are comparatively common in France. Buzzard and Wylie (1947) consider the clinical picture to be indistinguishable from other varieties of abacterial meningitis. Transverse myelitis and progressive paralysis have occasionally been reported. Fatal cases are usually associated with paraplegia.

Headache is severe and is associated with vertigo, mental confusion and Kernig's sign. Nystagmus and diplopia, iritis and irregularity of the pupils are common. Skin rashes of short duration are noted. In the cerebrospinal fluid the cell count and protein are increased, but

glucose and salt concentrations are normal.

In L. canicola infections the disease may be somewhat indefinite and jaundice is rare. Important diagnostic signs appear to be fever, conjunctivitis, appearance of a rash about the fifth day and symptoms of meningeal irritation. Canicola fever should be suspected in all cases of lymphocytic meningitis. In the form known as swineherd's disease caused by L. pomona meningeal irritation is predominant. "Canicola fever" is becoming increasingly recognized and over 70 cases have been diagnosed in England and Wales (Broom). It has been reported from Scotland (Jol and Sangster, 1951) and from N. Ireland by Kennedy, Crozier and Houston in 1953.

Complications.—Epistaxis, hæmaturia, melæna, hæmoptysis, deafness and pharyngitis have been noted as complications, and also inflammatory ocular changes, such as iritis and iridocyclitis. The secondary fever (after fever) or recrudescence with rigors may occur about the fourteenth or fifteenth day without recurrence of jaundice. During this stage a remarkable pyrexia may develop; in Japan it is seen in 30 per cent., and in Europe in 40 per cent. of cases and may last 14–24 days. The height of the fever is often greater than during the first febrile stage. There are many arguments against the view that this fever is a relapse, as all attempts to infect guinea-pigs with blood have been negative. It is generally

regarded as allergic, and due to absorption of toxins. The sequelæ are anæmia and debility. Alopecia usually occurs in convaloscence.

The mortality-rate may be fairly high—in the Andaman Islands about 18 per cent.

Diagnosis.—The urine from the fifth to the eighth day gives an intense green reaction when one or two drops of acetic acid are added. Early in the disease, if possible before the third day, the blood should be examined under the dark illumination for leptospires, and in doubtful cases should be inoculated into guinea-pigs for confirmation. For this purpose 6 ml. should be injected directly into the peritoneal cavity; citrated blood acts equally well, if not kept longer than twenty-four hours. The diagnosis may also be made, probably with more certainty, from the twelfth day onwards, by injection of the same quantity of catheterized urine. According to Fletcher, the diagnosis is most simply and readily made by direct inoculation of the blood into blood-agar, and subsequent incubation. Blanchard and Lefrou (1922) increased the chances of finding the parasite by triple centrifugalization of the blood. According to Schüffner, one centrifugalization of 10 minutes' duration at 1,500 revolutions is useful in demonstrating leptospires, when the plasma is separated from the precipitated red blood-corpuscles and then examined in a thick layer. Sheldon (1945) has drawn attention to the lesions of striated muscle first described by Pick (1917). Loss of striation and vacuolation of the fibres occur early and suggest muscle biopsy as a diagnostic test.

An agglutination test with cultures of leptospires grown on solid media is much used; it occurs in a titre of 1 in 500, 1 in 1,000, and even as high as 1 in 30,000 (Davidson, Schüffner et al.). The specific agglutinins appear in the serum as early as the sixth, more generally about the tenth day of

the illness, and persist for as long as twenty-two months.

Postmus (1933) found that this property of the serum may sometimes persist for eight years or longer. In carrying out the test Schüffner used living cultures of leptospiræ, and also cultures killed and preserved in formalin (0-2 per cent.). A small amount of gentian violet may be added to facilitate the reading of the results. One drop of antigen and various dilutions of serum are mixed in squares ruled on a slide, rocked for ten minutes, and then examined on a white background in diffuse transmitted light. On the whole, macroscopic agglutination test is less sensitive than the microscopic. For macroscopic agglutination test antigen is prepared from actively growing young cultures of leptospiræ. The volume of culture added is equal to six times the volume of each dilution of serum tested. The mixture of serum and culture should be incubated for three hours at 37° C., followed by thirty minutes at 55° C. With living leptospiræ agglutination appears only in the lower dilutions, as in the higher lysis sets in, rendering agglutination impossible. The one disadvantage is that the formalin mixture after some weeks is rendered useless by matting together of the leptospiræ into felt-like clots. The agglutination-absorption test was used by Schüffner and others as a means of differentiating strains of pathogenic leptospiræ; by these means he separated L. canicola of the dog.

Gardner (1947) uses rich cultures of living leptospiræ. Agglutination is observed with dark-ground illumination. With a 3-mm. loop a loopful of suspension is placed on a slide and 1-mm. loopful of 1:10 dilution of serum added

to make a dilution of 1:100. Preparations are best examined under dark-ground

illumination. Care must be taken to avoid auto-agglutination.

Brown and Davis demonstrated that the "adhesion" or Rieckenberg phenomenon is applicable to the diagnosis of Weil's disease as well as of trypanosomiasis. The reaction possesses distinct advantages over agglutination owing to the ease and certainty with which it can be practised. The test consists in allowing the immune serum to interact with the specific leptospira in the presence of a suitable indicator such as bacilli or blood-platelets. Not only can the disease be diagnosed by this method, but it may also furnish a means of differentiating leptospiræ.

The cultures used for the macroscopic agglutination test are obtained on Noguchi semi-solid medium by incubating at 32° C. for 5-7 days; 0.2 ml. of such a culture of actively motile leptospiræ is kept in a water-bath for one and a half hours at 37° C., mixed with an equal quantity of antileptospiral serum

and examined by dark-ground illumination for agglutination.

Gardner and Wylie (1946) used formolized serum-water cultures of the organism. For the culture a simple solution of 12 per cent. rabbit serum in glass-distilled water is most satisfactory (copper-distilled water is useless).

Gaehtgens elaborated a complement-fixation test. The antigen is a culture of leptospiræ, centrifuged, and the sediment suspended in saline containing

0.3 per cent. carbolic acid.

The centrifuged deposit of urine rich in these parasites may be utilized for an agglutination test in place of a culture, and the diagnosis has by these means been placed upon a scientific, if not on a practical basis. The leptospires can usually be demonstrated in centrifuged urine, and may be present up to the sixty-third day, though they generally disappear on the fortieth. Davidson has pointed out that their numbers are somewhat inconstant and they may disappear altogether in acid urine. If negative at first, this test should be repeated every second day up to the end of the third week.

An antiserum specific for the Leptospira icterohæmorrhagiæ has now been prepared from rabbits, and by this means the identification of the

organism has been made possible.

Randall and Cooper (1944) have found that the golden hamster (Cricetus auratus) is a test animal for the diagnosis of leptospirosis. Leptospires can be seen microscopically in peritoneal fluid withdrawn by capillary pipette 3-4 days after inoculation. Young hamsters, 3-4 weeks old, are susceptible to infection with L. canicola, but young guinea-pigs and mice prove comparatively resistant. Injection of centrifuged urine from an infected dog in 9-10 days produces death. This test can be employed for the differential diagnosis of L. canicola from L. icterohæmorrhagiæ infections since the hamsters succumb to both, whilst guinea-pigs succumb only to the latter. Schlossberger and Langbein (1952) have shown that L. icterohæmorrhagiæ can be transmitted through Ornithodorus moubata and can be demonstrated in its eggs.

From the fifteenth day onwards the immunity reaction may be employed; for this purpose 1 ml. of the patient's serum is left in contact, for fifteen minutes, with several times the lethal dose of the leptospira, and injected into a guineapig, which does not develop symptoms of the disease, while control animals die.

Differential diagnosis.—The disease has to be differentiated from yellow fever, infective hepatitis, catarrhal jaundice, syphilitic disease

of the liver, and the icterus of relapsing fever and of malaria. The fever must be distinguished from that of relapsing and of yellow fever, and the leptospira from Spirochæta recurrentis. On clinical grounds the diagnosis should not be missed, when jaundice, associated with nephritis and nitrogen retention, is followed by headache, muscular pains and scattered hæmorrhages. The difficulty in differential diagnosis between leptospirosis and yellow fever may be realized when it is remembered that the cases studied by Noguchi as instances of yellow fever were, almost certainly, cases of leptospirosis. Faget's sign is not present in leptospirosis (see p. 345).

In fevers such as typhus and cerebro-spinal fever, and in several others in which relapse may occur, including plague, rat-bite fever, and paratyphoid (especially paratyphoid-B), jaundice may be a complication. Other possibilities are lobar pneumonia, portal pyannia, and, occasionally.

Bact. coli septicæmia.

TREATMENT

- 1. General conduct of the case.—The systematic treatment consists in keeping the patient at rest, flushing out the bowel by repeated small doses of calomel, and intravenous injection of normal saline containing 5-10 per cent. of guesse. Should the nephritic symptoms become severe, intravenous injections of saline or of Ringer's solution, } to 1 litre. may become necessary. Williams (1947), in a case of renal failure with deep icterus, secured a cure by high spinal anæsthesia up to the level of the seventh dorsal. The results were dramatic and diuresis commenced with a good urea content of the urine. The urea concentration in the blood must be watched. The diet must be liquid and, if vomiting is persistent, should be given as nutrient enemata. For the pruritus accompanying icterus, anti-histamine compounds are recommended. If anuria develops the treatment of Bull, Jolkes and Lowe (1949) should be given. In this the fluid intake, which is reduced to the level of insensible loss, is provided by an emulsion of peanut oil and glucose in water. The diet, containing no protein or mineral salts, is administered by intragastric drip.
- 2. Penicillin treatment.—From 1944 onwards many papers have been published showing the specificity of penicillin for leptospira infections. The results in man have been based on experimental infections in guineapigs (Heilman, Herrell, Hart, Cross, Alston and Broom, 1944–45). Bulmer (1945) found that in man this was the most successful form of treatment, given in 40,000 units with an average amount of 1,125,000 units by continuous intramuscular drip, but it is essential that, to be successful, it should be given early, before damage to the liver or kidneys has taken place. All observers have been struck by the dramatic improvement after penicillin in 36 hours. In adequate doses it appears to shorten the general effects of the disease, as assessed by the duration of fever, but it does not affect the degree or duration of cholæmia as established by the icteric index and van den Bergh test. Therefore penicillin should be injected in all cases of Weil's disease as soon as possible and in high doses. Danaraj (1950) states that in 19 cases, including seven with

meningitis with changes in the cerebrospinal fluid, penicillin in does of 50,000 units was given every three hours for 7-10 days with beneficial effects. Broom, on further analysis, has criticized the results of penicillin treatment. No therapeutic results are reported from other antibiotics (Hall, Hightower, Diaz and others, 1951).

3. Antiserum treatment—An efficient serum is prepared by Burroughs Wellcome. This is given intravenously at intervals of several hours for at least four days in succession; 20 ml. at least should be given at each injection. For a man of 70 kg. weight, the dosage is 60 ml. daily for three to five days. Usually, after this treatment, the temperature begins to fall, but in advanced cases, in which jaundice and uramic symptoms have supervened, the method is of little value. Failing the provision of commercial antileptospiral serum, the serum of patients convalescent from this disease has been injected in daily doses of 30–40 ml. intramuscularly. To give the best results, this immune serum should have an agglutination and lysis titre of 1: 20,000, and this is reached 30–50 days from the commencement of the attack. It deteriorates when stored and should not be used after six months.

Prophylaxis.—Prophylaxis manifestly consists in sterilizing the fæcal and urinary discharges of the patients, and in waging war against the rat, the natural host of the parasite, and carefully guarding against its access to food. Swimming, especially the "crawl stroke," in pools or rivers known to be the source of the disease should be avoided. Sewer workers must protect themselves against abrasions. Noguchi prepared a vaccine of killed cultures of leptospires which he used for prophylactic inoculation in Japan.

SEVEN-DAY FEVER

Synonyms. Nanukayami; Shueki; Sakusku Fever (Japanese); Autumn Fever.

Definition.—A short fever, due to Leptospira hebdomadis and L. autumnalis, occurring epidemically during the summer months, especially in Japan (Fukuoka), characterized by sudden invasion, severe headache, pains in the back and limbs and pyrexia of a peculiar saddle-back, or occasionally of a continued type, lasting from six to seven days and associated with a relatively slow pulse.

History.—Possibly this is one of several fevers included under the term "simple continued fever." Its differential diagnosis from dengue was rendered clear by the discovery in 1918 of the *L. hebdomadis* by Ido,—Ito, and Wani.

Geographical distribution.—The home of the disease is Japan and Okinawa; it is found in China (Shan-si), and also in India, the Dutch East Indies and Australia, especially in dairy farmers. A disease of dogs in the Malay States was proved by Fletcher to be produced by a leptospire of the *L. hebdomadis* type.

Possibly also the organism described by Derrick (1942) in Queensland as L. pomona is related to L. hebdomadis and also L. autumnalis which was found in "Fort Bragg fever" in N. Carolina in 1944.

Ætiology.—L. hebdomadis and L. autumnalis resemble L. icterohæmorrhagiæ closely, but can be distinguished by serological reactions. These organisms are said by Noguchi to be slightly longer, the elementary spirals almost geometrically equidistant. They are present, though in small numbers, in the blood-stream during the pyrexial period, may be demonstrated by Giemsa's stain or by the

dark-ground illumination, and are readily cultivated by Noguchi's method. The chief channel of elimination is kidneys and urine.

The short-eared field-vole (*Microtus montebelloi*) appears to be the normal host of the leptospire in Japan, and the organism can be detected in the kidneys and urine of 3·3 per cent. of these animals, which can convey the disease by their bite. The endemic area of prevalence of seven-day fever corresponds with the distribution of this vole in Japan.

Microtus, sometimes termed a field-mouse, is really a stump-tailed field-vole, and is common in country districts in Japan. It burrows in the ground and feeds on roots and grain in much the same way as other small rodents.

The blood of convalescents from seven-day fever contains specific immune and leptospiracidal bodies and, when injected, together with a culture of the organism, into the peritoneal cavity of a guinea-pig, gives a positive Pfeiffer reaction. Young guinea-pigs are susceptible to inoculation with the blood of patients, and with cultures of the leptospire; they may also be infected via the skin or per os.

Symptoms.—The symptoms resemble those of Weil's disease but are much milder and are non-ieteric. The cases caused by *L. autumnalis* especially so. The blood shows a slight leucocytosis. The disease appears to be transmitted by the bite of infected field-mice, so that the patients are generally workers in the fields and forests.

After a short invasion-period the fever comes on briskly, and is accompanied by depression, muscular pains, especially in the calves, conjunctivitis, digestive symptoms, and enlargement of the lymphatic glands. Apparently, seven-day fever is a mild disease, has no mortality, and no distinctive pathological anatomy. The organism can be demonstrated in considerable numbers in the urine after the eighth day, and may persist to the thirty-ninth day. Albuminuria is noted in the early stages.

Differential diagnosis.—The disease is to be distinguished from relapsing fever, Weil's disease, rat-bite fever, and especially from dengue. There is considerable difficulty with dengue, for many writers have confused the two, and some consider them identical, but in view of recent work there can be little ground for adopting this view. The bone-pains and the morbilliform eruption in dengue suffice to distinguish it from seven-day fever.

Treatment.—The disease being generally slight, no specific treatment has been evolved. The fever must be treated on general lines. Penicillin treatment is of course indicated.

Note.—In Sumatra various observers have isolated leptospires from illnesses of different degrees of severity, including fevers of from one to five days' duration with no jaundice; more severe cases with jaundice; and finally, hæmoglobinuric cases resembling blackwater fever (see p. 65). The organism isolated from mild cases is morphologically identical with L. icterohæmorrhagiæ and may produce severe symptoms on inoculation into guinea-pigs. Vervoort (1923) proposed the name of L. pyogenes for organisms isolated from these fevers of short duration.

Fletcher in the Malay States also isolated leptospires from a variety of febrile cases, some resembling dengue, and he classified the organisms serologically into a number of groups. Owing to the instability of serological reactions, and the fact that primarily non-pathogenic water leptospires may he rendered pathogenic so as to produce symptoms of Weil's disease in animals, Baermann and Zuelzer reached the conclusion that all so-called pathogenic leptospiræ are identical with free-living forms in water.

The serotypes and serogroups of the numerous leptospires have recently been reviewed by Broom (1953). They form an extensive and complicated subject.

CHAPTER IX

RAT-BITE FEVER

Synonyms. Sodoku—so (rat), doku (poison); Sokosha (Japanese); Cat-bite Disease.

Definition.—An acute febrile disease caused by *Spirillum minus* (morsus-muris), inoculated into man by the bite of an infected rat (sometimes also cat and ferret) causing a local disturbance at the site of infection, followed by a general fever, with a tendency to relapse and, in some cases, a cutaneous eruption. "Cat scratch fever" is a different condition and is probably tularemia (Fox, 1952).

Geographical distribution.—Rat-bite fever appears to have a widespread distribution, but is especially common in Japan. Cases have been reported in Great Britain by Horder, Low, Atkinson, and Joekes, and in the United States, Germany, Italy, Australia, and East Africa.

Ætiology.—S. minus (Spirochæta m. muris; Leptospira muris) is a short, squat spirillum differing greatly from spirochætes, at any rate in the human body. It measures $1.5-6~\mu$ in length; the pointed extremities are continued into one or more flagella; including this, the total length may be $15~\mu$. (Fig. 35.) The curves are regular, and generally number three or four, or even six or more. It is difficult to demonstrate in the blood in the living state, even by the ultra-microscope, but it may be seen in the exudate in the neighbourhood of the bite, and in the juice from the superficial lymphatic glands.

In the living state the organism, under the microscope, moves rapidly like a vibrio, by lashing movements of the flagella; the body itself is held rigid, and in this manner the movements can be readily distinguished from the vibratile motions of the true spirochætes. This fact, together with a certain amount of doubt regarding its method of multiplication, has led to some controversy on its systematic position. The presence of the spirillum can be easily verified in suspicious cases by inoculation of white mice with any of the material in which it can be seen. Next to mice, white rats, guinea-pigs and monkeys (Macaca) are most susceptible. The spirillum can also persist in the blood of dogs without giving rise to any obvious symptoms. In mice, Ozeki has shown that the infected animals can be recognized within one or two months after infection by the loss of hair on the belly, chest and the nasal line, including the eyes and ears. Usually, however, experimental animals survive. The organisms appear in the bloodstream about seven days after inoculation, and persist for several months. The disease can be transmitted by the brown rat (Rattus norvegicus), the black rat (R. rattus and R. alexandrinus, R. r. kijabius (Heisch)), the bandicoot rat (Nesokia bandicota), the ferret or cat.

In Calcutta 2 per cent., in Venezuela 10 per cent., in Amsterdam 1 per cent., and in Toulon 18 per cent. of rats have been found infected. S. minus has not been found in the rodent's saliva, but the transfer seems to take place by a breach in the tissues through which the organism escapes, and is thus inoculated into the bite wound.

¹ By this magnification fine flagella appear to clothe the body of the organism.

The organism resembles, and is probably identical with, S. laverani and S. muris, which have been found in the blood of rats and mice in various parts of the world. Levaditi stated that in mice this infection is hereditary. Saisawa and Taise have shown that the spirilla can be found in large numbers in the peritoneal fluid of mice, and when these animals

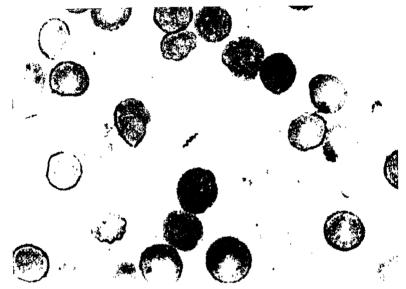


Fig. 35.—Spirillum minus of rat-bite fever in mouse. \times 2,500.

are treated with small quantities of neosalvarsan the organisms persist in the brain and in the spleen. Like the true spirochetes, they have the power of forming remarkable agglomerations, sometimes forming balls $40{\text -}50~\mu$ in diameter. Under the dark-ground illumination, these clumps move like a rolling ball.

Joekes has succeeded in cultivating S. muris, which he found in 25 per cent. of the wild rats in London, by using an inspissated horse-scrum slope, as employed for the diphtheria bacillus, over which is poured Vervoort's medium (1 per cent. peptone to which are added 3 c.c. of normal phosphoric acid). Primary culture is obtained by inoculating the medium with blood from an infected guineapig and incubating at 37° C. Subcultures are easily maintained in 1 per cent. glucose broth.

The immunity conferred on man and animals by an attack of this fever is permanent, and protects, apparently, against all other organisms of the same type that have been procured from various sources.

Although the general belief is that S. minus is the cause of rat-bite fever, it is necessary to state that there are some cases from which Streptobacillus moniliformis (Actinomyces muris) can be isolated on special media. In the United States it has been found that infection of wild rats with S. moniliformis (A. muris) is much commoner than with Spirillum minus. By some this is still considered to be the ætiological agent.

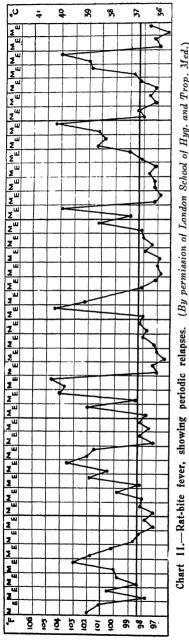
S. moniliformis (A. muris) first isolated in 1914, was shown by Parker to be

responsible for a milk-borne epidemic, "Haverhill fever." It is recognized in the U.S.A. that there are two rat-bite fevers, and that the one due to this organism is curable by intramuscular injections of 200,000 units of penicillin and streptomycin; one case (1948) is reported from Edinburgh from a bite of a laboratory rat by Lominski, Henderson and McNee. The latest work on this organism is by Waterson and Wedgwood (1953).

The differentiation of these two forms is summarized by Witzberger and Cohen (1944) as follows:-Sodoku Hazerhill Fener Transmission Bite of rat. Bite of rat or other animal. Possibly contaminated food. Incubation period 5-30 days. 1-10 days, average 5. Wound from bite Apparent healing, followed by Heals promptly. chancre-like ulceration. Lymph glands Regional lymphadenitis. Not involved. Systemic (a) Regularly relapsing type (a) Intermittent, but manifestations of fever. regularly relapsing type of pustular (b) Generalized maculo-(b) Macular, papular rash. petechial eruption. (c) Varying degrees of pros-(c) Varying degrees of prostration and debility. tration. (d) Arthritis very rare. (d) Metastatic arthritis fairly common. Laboratory Polymorphonuclear leuco-Same. findings cvtosis. Secondary anæmia. Same. Kahn test, usually +. Negative. Isolation of S. moniliformis by of spirillum Isolation by animal inoculation of blood culture and frompustules on veal infusion broth blood or infected gland. enriched with rabbit serum. Agglutination test negative. Agglutination tests with S. moniliformis positive. Serum agglutinates a polyvalent antigen of the bacillus. Responds to arsenicals and Arsenicals of little or no Treatment to penicillin. value. Curable with penicillin.

Pathology.—In inoculated guinea-pigs and white rats swelling of the lymphatic glands and spleen is observed. There have been few recorded human autopsies. Degenerative changes occur in liver and kidneys. In some cases increase of cerebro-spinal fluid and hyperæmia of the cerebral cortex have been reported.

Symptoms.—The incubation period varies from one to sixty days, the average being from five to ten days, during which time the wound heals. Then the cicatrix itself, and sometimes the surrounding tissues, become inflamed with formation of blebs and even necrosis. The lymphatics draining the area are implicated, and the glands themselves become swollen and tender. The supraclavicular lymph glands are specially affected (Heisch). The onset of the fever is characterized by rigors and malaise; the temperature gradually rises in three days to a maximum of 103–104° F., and, after a further period of three days, ends in crisis with profuse sweating.



spirilla in a thick blood-film.

After the primary attack a quiescent interval of five to ten days ensues, with subsidence of the local disturbance. One or more relapses (Chart 11), associated with the same symptoms and a characteristic purple papular exanthem, or urticaria, on the chest and arms, have been noted. The eruption is sometimes nodular. With each bout of fever the cicatrix at the site of the original bite becomes inflamed.

In most cases the reflexes are increased; there may be pains in the muscles and joints, hyperesthesia and ædema of various parts of the body. In some cases arthritis has been reported. The death-rate is about 10 per cent. In fatal cases the end is ushered in by delirium, often lapsing into coma. Some cases subside spontaneously: others go on for months.

As in relapsing fever, the organism can be demonstrated in the blood during the fever only, disappearing during the apyrexial intervals. The serum agglutinates the spirillum in low dilutions. There is an eosinophilia during the paroxysm and a moderate leucocytosis of about 15,000. It is said that the serum in this disease gives a weak positive Wassermann and Kahn reactions.

Diagnosis.—In many cases the diagnosis of rat-bite fever can be fully established from the history, the infiltration at the seat of the bite, the typical temperature curve, the rash, and the effects of the administration of neoarsphenamine or penicillin. This diagnosis can be confirmed either by dark-ground illumination, when spirilla may be seen in the exudate obtained from the site of the bite, or in the serous fluid from the papule, or by Giemsa-stained smears. It is seldom possible to demonstrate

If a number of relapses have occurred,

probably the best examination to make is for the presence of lytic antibodies. Absolute proof of the clinical diagnosis may be obtained by inoculating the patient's blood, lymph gland, or a piece of excised wound into guinea-pigs and mice.

Savoor and Lewthwaite demonstrated the curious fact that a well-marked rise in Proteus OXK agglutinins occurs in the blood of rabbits inoculated with S. minus, but in man, as well as in infected monkeys, the

reaction is negative.

Differential diagnosis.—This has to be made from the different forms of relapsing and trench fevers, with which the temperature chart has much in common. In tropical countries the possibility of a co-existent malarial infection has to be taken into account. The puffiness of the face accompanying the urticarial eruption may simulate Bright's disease.

The reaction occurring around the site of the scar is apt to be confused

with erysipelas or cellulitis.

Treatment.—Penicillin.—Lourie (1943) first showed that with penicillin S. minus disappears from the blood of experimental mice in 24 hours. These results were later confirmed by Heilman and Herrell (1944). It is equally efficacious against Streptobacillus moniliformis (A. muris). Oehme (1950) has reported the cure of rat-bite fever (by bite of water rat) by penicillin which was administered in doses of 25,000 units every three hours till one mega unit had been attained. A crisis occurred 12 hours later with fading of the rash. Salvarsan and its derivatives act as specifics. As a rule, one injection of neoarsphenamine (0·4–0·6 grm.) is sufficient.

Occasionally the intravenous injection has to be repeated as a prophylactic measure. A cat- or rat-bite should always be cauterized.

As in syphilis, so in rat-bite fever bismuth compounds appear to have a definite curative value, and in the fungus-infection (A. muris) streptomycin is indicated.

Prophylaxis.—Quite obviously, the prophylaxis of this disease, as in plague, rests upon efficient rat destruction. In Manila, for instance, it has been found that the distribution of rat-bite fever and plague are co-extensive and that therefore measures taken against one are in fact effective against the other.

¹ Neoarsphenamine is the name officially adopted in place of novarsenobillon, neosalvarsan, etc.

Subsection C.—FEVERS CAUSED BY BARTONELLA AND RICKETTSIA BODIES

CHAPTER X

BARTONELLOSIS

(OROYA FEVER AND VERRUGA PERUANA)

MEDICAL opinion in Peru has always regarded Oroya fever and verruga peruana as clinical manifestations of the same disease. For a time this view appeared to be negatived by the Harvard Commission in 1915, but the important work of Noguchi on the cultivation of the bodies of Oroya fever, and the subsequent production of verruga-like lesions on inoculation into monkeys, has established the unity of these apparently distinct diseases as generalized and localized manifestations of the same infection. Mayer and Kikuth in Germany fully confirmed the work of Noguchi.

OROYA FEVER STAGE (GENERALIZED BARTONELLOSIS)

Synonym.—Carrion's disease; "Guáitara fever."

Definition.—An acute specific fever, endemic in certain valleys of the Andes, characterized by a rapidly developing anæmia of the pernicious type, irregular pyrexia, and great tenderness over the blood-forming tissues. The organism is *Bartonella bacilliformis*.¹

History.—The first attempt to settle the ætiology of this disease was made by the self-sacrifice of Carrion, a medical student who, in 1885, fatally inoculated himself with the blood from a verruga nodule in Lima. From this experiment Peruvian physicians concluded that the verruga and Oroya fever were different stages of the same disease. Many thousands died of this fever during the reign of the Inca, Huayna Capac.

It is thought that Oroya fever was the disease which proved so fatal to Pizarro's army in the sixteenth century. Bours has recorded that all engineers superintending the building of the Trans-Andean railway contracted fever and half of them died of it. In 1906, out of 2,000 men employed on tunnel work, 200 perished. The monograph of Odriozola (1898) contains a classical account of this.

Geographical distribution.—Between the 9th and the 16th parallels of South latitude, and at an elevation of from 3,000 to 10,000 feet, in certain narrow valleys (quebradas) of the western slopes of the Andes, this peculiar fever is endemic. It is therefore found in Peru, Ecuador, Bolivia, Colombia, and Chile, and probably in Guatemala. A considerable outbreak occurred in the Guáitara Valley in South Colombia, near the Ecuador boundary, in 1936, mainly in the valleys of the Pacual, Juanumbú, Mayo and Sambingo, tributaries of the Rio Patía. Its topical as well as its geographical range is singularly limited; it is confined to certain hot, narrow valleys or ravines, the inhabitants of neighbouring places being exempt.

It is said that the disease may be acquired when merely journeying 'See the authoritative work, Infectious Anamias due to Bartonella and related red-cell Parasites, by D. Weinman, Trans. Amer. Phil. Soc., 1944, XXIII, Part III, 243-339.

through the endemic districts, more especially if the traveller passes the night there. Although out-of-door workers are the most subject, all ages, classes, and both sexes, including infants, are liable.

Ætiology.—During the fever certain rod-like bodies are found in a large proportion of the red blood-corpuscles (Fig. 36), and in endothelial cells of the lymphatic glands. These were noted in 1905¹ and again in 1909 by Barton, who considered them protozoal; his findings were subsequently confirmed by Strong and other members of the Harvard Commission who termed the bodies Bartonella bacilliformis. The organisms somewhat resemble stages of a piroplasm (Theileria parva) during its cycle in the lymphatic glands, and similar bodies are found in the blood of normal mice and certain rodents (Bartonella muris), which, as Mayer, Borchardt and Kikuth have shown, exist as a latent infection, but which may produce an acute and fatal anæmia, resembling Oroya fever, after removal of the spleen. (The causal organism of dog-anæmia following splenectomy is Bartonella canis. The clinical course of this infection is connected with an endothelial reaction, and the organism is transmitted by rat-lice (Hæmatopinus).)

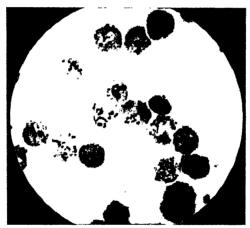


Fig. 36.—Blood smears with numerous Bartonella bacilliformis (human Oroya fever). (Kikuth.)

From the morphological standpoint, Bartonella and Rickettsia have resemblances. Both are minute, pleomorphic, Gram-negative and intracellular. On account of their peculiar behaviour, *Grahamella*, first described by Graham-Smith in the blood of moles, should be kept apart from *Bartonella* and regarded as a separate genus. In some repects they resemble *Pasteurella tularensis*.

Two forms of B. bacilliformis are recognized: one is a rod-shaped, slightly curved bacillary organism 2 μ long by 0.5 μ broad, staining with Romanowsky an intense blue, often in branching forms and in chains, but never crossed; the other is a rounded body about 1 μ or less in diameter, usually oval or pearshaped, and containing chromatin granules. Some occur singly, or end to end, in pairs or chains. V forms probably represent dividing organisms; Y shaped forms are also not uncommon. They are difficult to distinguish in fresh blood, and show feeble independent movement. Wigand and Peters (1952), using phase-contrast microscopy, have shown that in fresh blood they are feebly

¹ The first thorough description was given by Odriozola in 1898.

motile. When dried films are "shadowed" with palladium and examined by bright-field microscopy it is found that the organisms lie in depressions. By electron microscopy flagella are visible, each with diameter of 20 millimicrons,

in bundles, up to 10 flagella for each organism.

Noguchi regarded Bartonella as a bacillus and succeeded in cultivating it on solid media from specimens of citrated blood sent in "cold storage" from Lima to New York. The organism grows best at low temperature on bloodagar media. He was so successful in culture of the organisms that he recommended it in diagnosis as preferable to examining blood smears.

Battistini's method of culture is simple. A small drop of blood from the finger of the patient is withdrawn into serum-agar, or Noguchi's leptospira medium. The end is sealed in the flame and the whole placed in the incubator at 28° C. Colonies are visible in 5-6 days. B. bacilliformis is also readily cultivated in the allantoic fluid of the developing chick embryo at 25-28° C. The growth is rapid and abundant and the cultivated bodies are 0.6-1.6 u in length. Weinman and Pinkerton (1938) preferred the agar slant method devised by Linsser for cultivation of rickettsia. The bartonella is an obligatory aërobe and Gram-negative, but stains well with Giemsa. Intravenous injections of cultures into Macaca monkeys produce irregular fever and extreme anomia, whilst the organisms can be demonstrated in the blood-cells. Intradermal injection into the supraorbital tissues gives rise to nodules resembling verruga. In excised nodules Bartonella survives for at least fifty-six days at 40° C. Noguchi succeeded in conveying the infection to monkeys by the bites of ticks (Dermacentor andersoni). but Townsend in 1913 conjectured that the insect vector was a sandfly (Phlebotomus verrucarum). Further evidence incriminating P. noguchii and P. verrucarum was obtained by Noguchi and others in 1929, and this was confirmed in 1937 by Pinkerton and his colleagues. Insects were collected in a verruga district of Peru and sent in sealed glass tubes to New York. They were then ground up in saline and the emulsion injected intradermally into monkeys. The only insects which showed any evidence of containing bartonella were phlebotomi.

Hertig conducted transmission experiments in the laboratory with wildcaught phlebotomi from endemic zones. Five monkeys bitten by sandflies (Phlebotomus verrucarum) became infected with B. bacilliformis. As the result of extensive field studies on three species of phlebotomus, conducted for more than four years at different places and altitudes in Rimac and Santa Eulalia Valleys, it now appears that P. verrucarum (not P. noguchii) is the most important

transmitter.

Hertig has also described a curious infection of the tip of the proboscis in both male and female Phlebotomus captured in the Peruvian verruga zone. From these B. bacilliformis has been recovered by culture and also an unnamed micro-organism of similar morphology. The proportion of sandflies so affected may be from 40-50 per cent. In many instances the pharynx of the sandfly is also infected. Since this condition has been found in male insects which do not suck blood, as well as in females which have never had a blood meal, the possible relationship to Carrion's disease remains obscure.

The Neill-Mooser scrotal reaction is produced sometimes by inoculation of guinea-pigs with blood of Oroya fever or with cultures of B. bacilliformis.

If present, it is well-marked on the third day.

The disease is most prevalent from January to April, when the streams are in flood, the air hot, still, and moist, malaria epidemic, and insect life abundant.

Pathology.—A remarkable feature of this disease is the rapid and extreme blood destruction. In bad cases the blood-count may drop in three or four weeks to 500,000 per c.mm., the picture being that of a pernicious anæmia. There is a marked polymorphonuclear leucocytosis with disappearance of eosinophiles. The red cells are of the megalocytic type.

In addition to the anæmia, marked changes are present in the liver, spleen, and bone-marrow. In the liver, areas of degeneration and central necrosis are found around the hepatic veins. In the centre of the necrotic areas a yellow pigment resembling hæmosiderin is present in abundance. The spleen is invariably enlarged, and also contains necrotic areas with pigment in the pulp, but the Malpighian bodies themselves are not affected. The lymphatic glands contain large macrophage endothelial cells studded with rod-shaped bodies. B. bacilliformis commonly occurs in closelypacked masses in swollen endothelial cells, especially those of the lymphatic glands, spleen, liver and intestines. The lesions in the viscera are considered by Strong to be due to toxins liberated by the parasite. The bone-marrow shows proliferation, necrosis, and marked phagocytosis of the large endothelial cells. Noguchi observed in monkeys succumbing to bartonella infection the same lesions as have been recognized in man-in the spleen and also in the lymphatic glands, endothelial cell hyperplasia -in the bone-marrow an increase of macrophages, and in some instances, normoblasts.

Symptoms.—The incubation period of Oroya fever is about three weeks. Its onset is insidious and is marked by malaise, soon followed by a rapidly developing pernicious anæmia and an irregular remittent pyrexia, associated with very severe pains in the head, joints, and long bones. The bone pains are probably connected with the disturbances in the hæmopoïetic system. Very often the initial fever is like that of malaria and may be the outcome of a superadded infection in a malarial subject. The most severe types resemble fulminating typhus and are known as the "severe fever of Carrion." The liver and spleen are enlarged and tender. The anæmia develops with great rapidity. The death-rate varies from 10 to 40 per cent. of those attacked, the end coming within two or three weeks of the onset of the disease. A terminal delirium is often noted. In those cases which progress to the verruga stage, the fever may last three to four months. Secondary infections with Salmonella organisms often prove fatal.

Howe has shown (1945) that immunity to this disease is rapidly acquired,

but bears no relationship to specific agglutinins in the blood.

The Harvard Expedition to Peru in 1937 recognized three types of Carrion's disease.

(1) the anæmic;

(2) the asymptomatic; and

(8) the cutaneous, reproduced by inoculation of (a) infected lymphnodules, (b) human verruga tissue, (c) cultures of bartonella.

Treatment.—Penicillin.—Merino has reported favourably on two cases, the only ones so far published, a total of 300,000 units, in doses of 25,000 every three hours. The first four injections were given intravenously, the others by the intramuscular route. The temperature dropped immediately. Payne and Urteaga have used chloromycetin and

the fever subsided within 48 hours. B. bacilliform is assumed a coccoid form in 24 hours. There was a marked reticulocytosis and a rapid return of the blood to normal. Kikuth produced an arseno-antimony compound, Sdt. 386 B which is said to have a selective action for bartonella. The therapeutic index is very high and the margin between the dosis tolerata and toxica wide. Manrique reported results in twelve severe cases treated with intravenous doses of 0·1·0·3 grm, repeated two to three times. He succeeded in banishing bartonella from the blood-stream and bringing about a rise in the blood-count. A total of up to 5-7 grm, of this drug was injected without causing any systemic disturbance. The general opinion of Peruvian physicians is that severe infections are not influenced either by this method or by blood transfusion. An immune rabbit serum has been produced by Howe (1943), but is apparently ineffective in treatment.

Prophylaxis.—A prophylactic inoculation with formolized suspensions of *B. bacilliformis* has been introduced by Howe (1943) and has resulted in production of partial immunity in so far that any subsequent attack of Oroya fever is modified.

VERRUGA PERUANA STAGE (LOCALIZED BARTONELLOSIS), OR ERUPTIVE STAGE

Definition.—A remarkable granulomatous eruption confined to certain parts of Peru, Colombia and Ecuador (Montalván and Moral, 1940). It is associated with hæmorrhages, fever and joint pains. The disease was known to Pizarro, and is described in Prescott's "Conquest of Peru."

Ætiology.—Superficially, the lesions of verruga resemble those of yaws. Rocha Lima, Mayer, and Werner described chlamydozoa-like cell inclusions in the verruga nodules and considered them to be the cause of the disease. As already related, Noguchi demonstrated bartonella bodies in experimentally-produced lesions in monkeys. This work was confirmed by Mackehenie, Weiss, Mayer and Kikuth, who produced nodules in monkeys with human material and demonstrated bartonella bodies within angioblasts or endothelial cells. Verruga is therefore a local connective-tissue infection with Bartonella bacilliformis.

Strong's experiments on monkeys showed that graduated inoculation of verruga material induces an artificial immunity. Verruga can be conveyed by inoculation to rabbits and puppies and, according to Townsend, occurs as a natural infection in native American-Indian dogs.

Pathology.—Primarily, the pathological changes consist in proliferation of the endothelium of the lymphatic channels which become obstructed by plasma-cells and fibroblasts, but the structure is much more vascular than that of yaws which it otherwise resembles. The capillary blood-vessels become dilated, so that the granulomatous tumours are vascular, almost cavernous and apt to bleed profusely. A feature of the pathological histology is the formation around the blood-vessels of nodules of angioblasts characteristic of the disease. In the endothelial cells of cutaneous verruga nodules B. bacilliformis may be seen in considerable numbers, but distension of the cells is less than that seen in Oroya fever

cases (Jiminez and Buddingh). Bartonella bodies may be found in the blood-corpuscles after prolonged search (Mayer), but in monkeys, if the spleen be removed, they multiply exceedingly and produce Oroya fever.

Symptoms.—The period of incubation subsequent to Oroya fever is thirty to forty days, but in those cases in which the initial fever is absent it is at least sixty days. Although verruga is usually a sequel of acute bartonellosis, it may arise spontaneously and independently of Oroya fever. The initial stages are characterized by peculiar rheumatic-like pains, together with fever, the pains being apparently like those of yaws, only more severe. As in yaws, the constitutional symptoms subside on the appearance of the skin lesion. The eruption, like that of yaws (see p. 605), may be sparse or abundant, discrete or confluent. As in yaws, individual granulomata may fail to erupt; others may subside rapidly; yet others may continue to increase, and then, after remaining stationary for a time gradually wither, shrink, and drop off without leaving a scar.

The eruption is generally described as of two types, miliary and nodular—the former not exceeding the size of a small pea; the latter, the rarer, less numerous, but consisting of much larger nodular masses. The

miliary eruption, as a rule, is found most abundantly on the face and extensor aspect of the extremities, less commonly on the trunk (Fig. 37). A pink macule first appears, which later darkens and becomes nodular. These nodules may be flat or somewhat pedunculated. The verruga artificially produced in monkeys by injection of bartonella bodies is bright cherry pink.

In yaws we find no mention of fungating granulomata in any situation but in the skin. In verruga it seems that these vascular lesions may develop on mucous surfaces—in the mouth, œsophagus, stomach, intestine, bladder, uterus, and vagina. Hence the dysphagia—a common symptom—and occasional hæmatemesis, melæna, hæmaturia and bleeding from the vagina. Relapses both of the fever and of the eruption may occur.

In inoculated monkeys swelling of the lymph-glands is an early and constant symptom.



Fig. 37—Verruga peruana. Miliary form from Ecuador. (Dr. L. A. Léon.)

The nodular eruption is more chronic than the miliary. Individual lesions may grow to the size of a pigeon's egg; they may become strangulated and a source of danger from hæmorrhage. This type does not

invade the mucous membranes and is usually confined to the regions of the knees or elbows. It appears in crops and lasts two or three months. In contrast to Orova fever, the mortality from verruga is practically nil.

Diagnosis.—The appearances of verruga are so characteristic that it is hardly likely to be mistaken for any other disease. Conceivably, it may resemble the frambæsiform eruption of secondary yaws; it may also be simulated by multiple warts, molluscum contagiosum, multiple fatty tumours (Dercum's disease) and, according to Strong, it is closely allied to, if not identical with, Bassewitz's angio-fibroma cutis conscriptum contagiosum. Individual tumours may resemble fibro-sarcoma or angioma. The Oroya and verruga stages frequently coexist.

Agglutination reaction.—Suspensions of B. bacilliform is are obtained on media devised by Geiman. Sera from patients were found by Howe to agglutinate the organisms in titres from 1:10 to 1:80 in both the Oroya fever and verruga stages. A co-agglutination is usually found with cultures of $Proteus\ OX19$, OXK and OX_2 . A strong agglutinating serum for testing cultures of B. bacilliform is has been produced by intravenous injection of rabbits with living cultures.

Treatment.—Very little is known about the treatment of this condition. Small doses of salvarsan, 0·2 grm. intravenously, have been tried with benefit. From what is already known of the action of penicillin and chloromycetin on bartonella these anti-biotics are indicated. When individual tumours begin to ulcerate, or become gangrenous, they should be excised. Dangerous bleeding may occur, and styptics or compresses may be required to stay excessive loss of blood.

CHAPTER XI

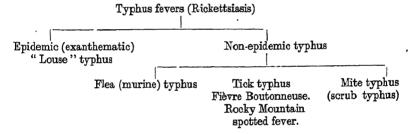
THE TYPHUS GROUP OF FEVERS

Preliminary statement.—Typhus fevers have an almost worldwide distribution, but do not manifest themselves as one definite entity throughout their range. They are divisible into a number of local forms which have become stabilized in type. These forms, or varieties, are probably adapted to local conditions or in some way connected with those arthropod intermediary hosts which convey the rickettsiæ. The student who is interested in the romance of this interesting subject should consult Zinsser's "Rats, Lice and History" (1935).

Classical typhus should be called louse-borne "true" or "exanthematic typhus" and the local varieties be known by their descriptive pseudonyms—murine typhus, scrub typhus, Rocky Mountain spotted fever, Fièvre

boutonneuse, etc.

The following primary classification somewhat clarifies the situation:



Other forms of tick typhus are South, West, and East African, Indian, South-East Asian, Western Siberian, Northern Queensland.

Ætiology of the group.—Rickettsiæ are Gram-negative bacteria-like bodies, usually less than 0.5μ in diameter. There are at present eight named species and several varieties. The organism originally named Dermacentroxenus rickettsii by Wolbach, first described by Ricketts (1910), and now known as Rickettsia rickettsii, is the causal agent of Rocky Mountain fever. The rickettsia of louse-borne typhus was named R. provazeki by da Rocha-Lima (1916) in honour of two distinguished investigators (Ricketts and Prowazek) who both succumbed to the disease, and the latter of whom was the first to recognize their true nature. Topfer (1916) described rickettsia in lice removed from patients suffering from Volhynian fever (trench fever), but this is now known as R. quintana (R. volhynica). Sellards (1923) distinguished the organism of tsutsugamushi disease in Japan as R. orientalis (=R. tsutsugamushi, R. nipponica). The organism of flea-borne typhus is R. prowazeki, var. mooseri (=R. muricola). The causal agent of fièvre boutonneuse is sometimes known as R. conori. The rickettsia of "Q fever," R. burneti (now known as Coxiella burneti, Parker, 1949), a comparatively recent discovery by Burnet and Freeman (1985), has a wide range in Australia, North America and Europe, and is of much greater importance than was at first realized. Rickettsialpox in New York is due to R. akari.

Trench fever, Q fever and rickettsialpox although classifiable as rickettsi-

ases, do not strictly belong to the typhus group.

Rickettsiæ are found commonly in the alimentary tract of blood-sucking and non-bloodsucking insects but, probably, they were primarily parasitic in the cells lining the canal, as is the case with R. prowazeki. For instance, R. pediculi is an extracellular organism which is an inhabitant of the gut of the louse, is harmless to its host and also to man, resembling

R. quintana which develops in the same manner and situation.

The cycle of development of R. provazeki in the louse consists primarily of great multiplication in the midgut, both in the lunen as well as inside the epithelial cells, which become distended. After a few days these rupture and rickettsiæ appear in large numbers in the faces; this rickettsial invasion killing the louse in about ten days. The blood of typhus patients is infectious for the louse from early in the disease till the tenth day—occasionally later, even when the patient is afebrile. The disease therefore is conveyed to man by louse faces through abrasions in the skin, or even through the conjunctiva; possibly also by inhalation. Louse faces kept dry at room temperature have been proved to be infective for 66 days. There is no hereditary transmission, whilst louse eggs do not contain the virus. A possibility exists that "clean lice" may themselves be contaminated by the excreta of other typhus-infected lice when feeding.

R. prowazeki, var. mooseri (R. muricola), is normally transmitted from rat to rat by the rat louse (Polyplax spinulosa) and by the tropical rat mite Bdellonyssus (Liponyssus) bacoti. In these insects the cycle is similar to that already described in the louse. The species of flea mostly concerned is Xenopsylla cheopis, but in this instance the infection causes it no appreciable harm. X. astia may also act as a vector. In the faces of the flea rickettsiæ remain alive and virulent for long periods—40 days in the dark and 100 days in vacuo. Zinsser and other authorities regard flea typhus as the original pristine form of human typhus, but this is by no means certain.

The cycle of development of rickettsiæ in ticks follows on much the same lines, but is much more widespread. The rickettsiæ invade the cells and their nuclei; they are found in all tissues, including the ovaries of the female tick, so that the infection is transmitted hereditarily. Rickettsiæ are also found in the salivary glands so that infection is commonly conveyed by the bite of the arthropod. The similarity of the clinical appearances of various forms of tick-borne typhus is undoubtedly close in widely separated geographical regions. In only one particular can they be said to differ—in the absence of a primary lesion in Rocky Mountain spotted fever and its presence in other types.

Zinsser has pointed out the importance of the hereditary factor in tick-transmission as indicating a very ancient condition, producing a mutual tolerance, so adjusted that neither the well-being of the animal

reservoir nor of the tick intermediary is impaired.

The mode of transmission of the rickettsia from animals to man, or

from man to man, and the relationship of the various forms of typhus to one another can be expressed as follows:

Epidemic louse-borne typhus .	Man—Louse—Man
Murine Typhus	Rat Rat Flea Rat.
	Rat—Flea—Man. Rat—Flea—Man—Louse—Man (pos-
Tsutsugamushi. Scrub Typhus (Mite	
Typhus) Spotted Fever Types (Rocky Mountain	?Rat or Field Mouse—Mite—Man.
Spotted Fever). "Tick Typhus." Fièvre Boutonneuse. S. African tick-bit.	Rodents (Gopher)—Tick—Tick—Man.
	Des Mish Mish Man
fever Q Fever	The Transfer of the transfer o

Morphology.—In their morphology in human tissues (Wolbach and Todd) rickettsiæ appear as small bacilli or cocci, very variable in arrangement. Diploid forms and also coccoid forms in dense masses are common.



Fig. 38.—Rickettsia prowazeki, var. mooseri. ("Mooser cell.")
Tunica vaginalis of guinea-pig infected with murine typhus from wild rate.
Oytoplasmic nekettsise invading a mononuclear cell. Giemsa stain.
Approx. × 4,000 (Anigstein and Bader. Galveston, Texas).

With the possible exception of R. tsutsugamushi they stain well by Giemsa's method, and blue with Castañeda's stain (Fig. 38). None of the species

can readily be cultivated on solid media (p. 256). Practically pure strains of *R. prowazek* are obtained by intrarectal injection of lice with infected material, as practised by Weigl, but attempts to culture them from human tissues have so far been unsuccessful. All rickettsiæ grow readily on the chorio-allantoic membrane, or preferably in the yolk sac, of the developing chick embryo, whilst Gispen (1941) has shown that ducks' eggs are highly suitable. The rickettsiæ do not cause death of the embryo, though they produce big, round, prominent foci five days after inoculation and develop completely in 7–8 days. They grow in tissue cultures and in a medium of minced chicken embryo with a mixture of guinea-pig or rabbit serum and Tyrode solution.

In all laboratories in which work is done with typhus rickettsiæ workers are liable to attack, in spite of previous inoculation, so that vaccine cannot completely protect against infection by the respiratory route that occurs in these cases, though it greatly reduces the severity of the attack.

Such an outbreak has been reported in London by Van den Ende and others. Eleven cases could be attributed to inhalation of infective droplets during intranasal inoculation of mice under ether anæsthesia. In the remaining cases dust may have been the source of infection.

Although there is evidence that rickettsiæ will grow in the presence of non-living cells, yet they require their presence and thus resemble viruses rather than bacteria which can be grown on artificial media. With the exception of R. (Coxiella) burneti, pathogenic rickettsiæ are difficult to filter through Seitz or porcelain filters. Rickettsiæ can be grouped provisionally between the true viruses and bacteria.

Pinkerton has pointed out that the two main forms of typhus—the louse-borne and the tick-borne—may be differentiated by the cellular re-

action they produce.

Typhus, conveyed by lice and fleas, usually during the winter months, is characterized by invasion of the endothelium and mesothelium by rickettsiæ, producing distension of the cytoplasm of the host cells without affecting the nuclei, while in guinea-pigs it causes proliferative endangiitis without thrombonecrosis. In typhus-infected lice and fleas rickettsiæ are intracytoplasmic, inhabiting the lining cells of the gut; they are not hereditarily transmitted.

The spotted fever group, conveyed by ticks, is characterized by thrombonecrosis of arterioles and venules. The rickettsiæ in human tissues invade smooth muscle cells, endothelium, mesothelium and histiocytes. In tissue-cultures a massive infection of the nuclei takes place. In infected ticks the organisms are intranuclear as well as intracytoplasmic, invading nearly all types of tissue and they are hereditarily transmitted. These are suggestive distinctions.

Differential reactions.—The Neill-Mooser reaction is a distinctive reaction in guinea-pigs inoculated with typhus blood. A redness and swelling of the scrotum appears and typical typhus lesions are found in the scrotum in the endothelial lining of the tunica vaginalis; swellen cells packed with rickettsiæ are seen in sections. Some strains, notably



R. rickettsii, give this reaction more strongly than others; it is also present in about 70 per cent. of epidemic typhus in early guinea-pig passage and nearly always in the murine type. Raynal and Fournier have pointed out that a somewhat similar orchitic reaction may be caused by Salmonella paratyphic B., and also by Spirillum minus, but the reaction produced occurs later, lasts longer and the scrotum is harder.

AGGLUTINATION REACTIONS AS A MEANS OF DIFFERENTIATION

The only serological test formerly available was the Weil-Felix reaction, using strains of proteus known as OX2, OX19 and OXK. While louse-and flea-borne typhus gave positive agglutination with OX2 and OX19, mite-borne typhus reacted with the OXK (K for Kingsbury) strain. The Weil-Felix reaction was by no means specific, for cases of undulant fever, relapsing, and ratibite fever give a positive agglutination reaction, more especially with OXK. Suspensions of Proteus OXK are liable, especially in the tropics, to become unsuitable for performing agglutination tests. It should be remembered that in those inoculated against typhoid or paratyphoid fever the onset of typhus may cause a rise in the agglutination titres against Salmonella typhi and S. paratyphosum A. and B. Diagnosis is now made by agglutination of rickettsial suspensions and by complement fixation, using rickettsiae from the infected yolk sac of the developing chick embryo as antigen.

1. EPIDEMIC OR LOUSE-BORNE TYPHUS

Synonym.—True exanthematic, historic, or classical typhus; Tabardillo (Mexico). Chronic form: Brill's disease.

Definition.—An acute fever, louse-borne, abrupt in onset lasting about fourteen days and, if not fatal, terminating by crisis about that time. The pyrexia is remittent. On or about the fifth day there appears a roseolar eruption tending to petechiæ spreading from the abdomen over the trunk and extremities. As was stressed by Zinsser and MacArthur, this form of typhus must be considered the most important disease in history.

Geographical distribution and epidemiology.—Typhus is worldwide. Still common in E. Poland, N.W. Soviet Russia and Ukraine. (Between 1917-1928, 30,000,000 cases with 3,000,000 deaths in European Russia.) India, N.W. Frontier, N. Africa, N. Nigeria, Belgian Congo, E. and S. Africa, Cochin China, Central and S. China, Korea, Manchuria, Sumatra, Philippines, N.E. Australia, Japan, Mexico, and Abyssinia. Formerly frequent in England and Ireland. (In 1942 a limited epidemic occurred in Galway, Eire (Stuart-Harris and others).)

In 1932 there was a big outbreak in Uganda, especially in districts of over 5,000 feet altitude. Similar occurrences have been reported in the

Himalayas and Afghanistan.

Typhus can thus occur in tropical countries as well as in those with a cold climate.

There was a new wave in 1933 in Egypt and Chile, in 1934 in South Africa, in the Soviet Union, Rumania, Poland, Yugoslavia, Portugal and Hawaii. Typhus is most frequent in winter and spring months when heavy clothing affords an opportunity for lice-breeding.

Etiology.—Rickettsia prowazeki, the specific organism, is conveyed by the louse (Pediculus humanus, var. corporis and capitis); in the blood during the first five days it is filterable and infective for monkeys and guinea-pigs as the rickettsiæ are present in the blood-plasma, especially in the blood-platelets. A development cycle of the rickettsia takes place in the intestinal tract of the louse (see p. 256). Infection is conveyed by the louse fæces, which are inoculated into scarified skin by scratching. Löffler and Mooser (1942) showed that head-lice play an important part in transmission.

Typhus blood was found infective for guinea-pigs and monkeys by Ricketts, Nicolle and Anderson; later Wolbach, Todd, Palfrey and Pinkerton (1920-22) found intracellular *R. provažeki* in lice in Poland. Nicolle, Compte and Conseil proved by experiment that the chimpanzee can be infected by lice.

Weyer states that the meal worm—the larva of *Tenebrio molitor*—is susceptible to infection with *R. prowazeki* (also with *R. mooseri* and *C. burneti*) when inoculated into the colonic cavity, but no change in virulence is produced.

Multiplication of the rickettsiæ in the meal worm takes place specially in the non-differentiated cells, within young fat cells, whilst large numbers

are found in the phagocytes.

So many physicians died of typhus during the 1914-1918 war and so many contracted the disease that other methods of transmission than by lice were suggested and it is probable (as accepted in the second world war) that the rickettsiæ may also be conveyed as a droplet infection. There are German reports that infection has been acquired by medical attendants while taking blood for the Weil-Felix reaction. Typhus has also been conveyed by blood transfusion when the donor happened to be in the incubation period of the disease.

Pathology.—The rash is usually visible after death. There are conjunctival hamorrhages and, as a rule, areas of skin necrosis and gangrene. The blood is particularly dark and does not clot. The kidneys and liver show cloudy swelling. The spleen is usually moderately enlarged, with hyperplasia of the lymph follicles; the substance is soft and diffluent. Bronchial catarrh is usually present, with hypostatic pulmonary congestion.

The eruption is due to proliferation of the endothelium and localized necrosis of the walls of the smaller blood vessels, with local collections of lymphocytes and plasma cells in the adventitia. These are the "typhus nodules" which resemble miliary tubercles, first described by Frænkel and subsequently by Aschoff, Wolbach and others. They are characteristic, and are found in the vessels of the skin, myocardium, brain and viscera (Fig. 39). The essential lesion is due to phagocytosis by cells of the vascular endothelium, followed by necrosis of those which enclose rickettsiæ and their toxins. Lesions in the brain, resembling

miliary tubercles, are found especially in the basal ganglia, medulla and cerebral cortex.

The red marrow becomes hyperplastic and is converted into yellow marrow, though there is little increase n the myeloid elements.



Fig. 39.—Typhus module. Section of arteriole of skin showing attached mural thrombus, composed almost wholly of phagocytic endothelial cells, with early proliferative perivascular reaction.

(After Wolbach and Todd.)

Symptoms.—It has been said that the more clinicians see of typhus the more varied becomes the clinical picture. The disease varies within wide limits. A particularly mild or larval form was originally described by Brill in 1898 amongst the Jewish population of New York (Brill's disease). The infection was brought in by immigrants from the typhus regions of S.E. Europe, so that 90 per cent. of cases occurred in foreign-born people.

Its incidence is sporadic and it is now regarded as the inter-epidemic form of epidemic, louse-borne typhus. The best designation is probably "recrudescent epidemic typhus."

The incubation period varies between five and twenty-three days, the average being twelve. The period of onset lasts about two days, during which the patient has rigors, headaches, pains in back and limbs, nausea and giddiness. Vomiting is frequent. Occasionally, fulminant cases (typhus siderans), with general convulsions and delirium, are met. On the third day the temperature rises suddenly to 103° or 104° F., the face becomes congested, with general suffusion of the eyes. The headache is very severe (German—Kopfwehkrankheit) and with it goes a peculiar stuporose, drunken look not seen in any other disease except,

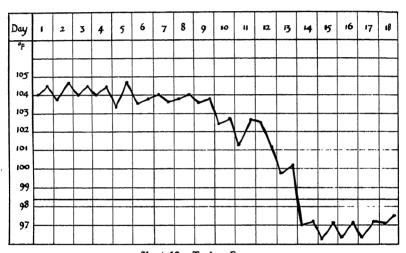


Chart 12.-Typhus Fever.

perhaps, plague. The patient is drowsy, often delirious (coma-vigil), usually with insomnia.

The mouth is foul, the tongue coated with a dense brown fur, the breath offensive. Epistaxis is frequent in the early stages and vomiting may be distressing. For twelve to fourteen days the temperature remains raised with slight, sometimes scarcely perceptible, morning remissions (Chart 12). The urine is concentrated, offensive, with a cloud of albumin, urea and chlorides initially increased in amount. In severe cases there is often hæmaturia. The spleen is usually enlarged and palpable. German observers lay great stress on the changes in the cardio-vascular system, especially the low systolic and diastolic blood pressures.

The rash, so characteristic of typhus, may appear as early as the third day, but more usually on the fifth or sixth, upon the abdomen, inner aspect of the arms, spreading over the chest, back and trunk, usually pleomorphic, involving the face only in severe cases. It may be absent in about 10 per cent. The term "mulberry rash" is usually

employed to describe it, but it essentially consists of roseolar macules, with fine, irregular dusky mottling underlying the epidermis, best described in the words of Murchison as "subcuticular mottling." Usually it becomes petechial and may then be seen especially on the hands and soles of the feet (Fig. 40).

Rarely, it is bright red, instead of a mingling of copper and purple; sometimes, too, it may be hæmorrhagic. Papular spots are commonly encountered and may be circular or indefinite, but when petechial they may closely resemble flea bites. The rash fades very slowly and may



Fig. 40.—Typhus rash in second week, showing typical distribution. The dark coloured areas are petechial; the lighter coloured, less discrete areas disappear on pressure.

(After Wolbach and Todd.)

remain visible for ten days. A fine brawny desquamation towards the end of the third week has been described; it sometimes occurs on the soles of the feet.

In dark-skinned natives the typhus rash is necessarily very difficult to discern. To make the subcuticular mottling visible, a thorough cleansing of the skin and a good light are necessary. Congestion of the upper arms by a tourniquet, such as the band of a blood-pressure apparatus, usually renders the petechiæ more easily visible. This method has also been practised with success in the early diagnosis of the typhus rash in Europeans. In natives the rash is usually more pronounced around the umbilicus.

On the appearance of the rash there are usually signs of bronchitis and in severe cases sometimes icterus; prostration and cardiac weakness become more pronounced, and with increase of the mental lethargy the patient sinks into the "typhus state." The expression becomes dull and vacant, the face flushed, with a peculiar earthy hue (facies typhosa). Cerebration is slow; the hands and tongue are tremulous and the patient becomes more difficult to nurse. The skin at this stage sometimes emits an odour which has been compared to that of "gun-washings," or that emanating from a cupboard containing well-blackened or mouldy boots.

During the second week a low muttering delirium usually supervenes. Meningism is not uncommon. The secretion of urine may then be diminished or even suppressed. Often symptoms of cortical irritation, such as muscular twitchings, and incontinence of urine and faces may be observed. The cerebro-spinal fluid is under pressure and there is usually an increase in the cell content. It is estimated that 80 per cent. suffer from all degrees of deafness. Especially common are septic infections of the middle ear which usually appear from the sixth to eighth day (Mittermaier).

In severe cases the pupils become pinpoint and the eyes "ferrety" As the fourteenth day approaches, signs of improvement may set in ; the temperature falls by crisis, or sometimes by rapid lysis. Death generally occurs on the twelfth or fourteenth day, or it may be later, when the temperature is subnormal, from exhaustion or cardiac failure. The blood picture usually shows nothing very definite, but a moderate leucocytosis of 12,000 to 15,000 per c.nun., mostly of large mononuclear cells, is not unusual. The blood is concentrated so that the hemoglobin

and red blood count are abnormally high.

Amongst indigenous populations terrible complications due to sepsis and neglect may ensue. Terminal bronchopneumonia is common. The patients become extremely emaciated. Involvement of the central nervous system is frequent, such as ataxia, violent tremors, mania or dementia. Hemiplegia or paresis of the limbs due to typhus nodules in the brain has been reported. Parotitis and noma are frequent. Abortion in pregnant women is common. Constipation rather than diarrhea is the rule. The mouth becomes very foul, with the lips and teeth covered with sordes. Bedsores are frequent. Thrombosis of the femoral vein is not uncommon, while gangrene of the extremities, especially of the toes or scrotum, due to arterial thrombosis, is frequently seen in wartime epidemics. One of the most distressing features is gangrene of the lung as a termination of typhus bronchopneumonia. Mental symptoms are among the most important sequelæ. Recently it has been suggested that juvenile thrombo-angiitis obliterans (Bürger's disease) may be due to antecedent typhus.

Relapsing fever and typhus frequently co-exist and this superadded infection is serious. Mild forms of typhus, lasting some ten days, are frequently seen in children, but it is usually the very young, the aged and the ill-fed who most readily succumb. Aberrant forms of typhus fever without a rash may be encountered towards the end of an outbreak when

immunity is high.

Convalescence is usually slow and prolonged, and during this period

great care should be taken not to excite the heart. Snapper pointed out that thrombocytopenia is not infrequent in typhus and some cases, even after the typhus infection is over, show a typical anaphylactoid, sometimes even a thrombocytopenic purpura. Loss of hair on the head and legs is said to be common.

The case mortality is negligible in children. It is 10-15 per cent. up to the age of forty, but 50 per cent. at fifty; over that age few survive. Relapses of typhus have been recorded. It appears that epidemic typhus has become so solidly established in man that some individuals, who have recovered from a first attack, retain the rickettsiæ in their bodies and may develop a second many years after the first, at such time as when the bodily resistance is depressed.

Immunity.—On recovery from an attack of typhus the immunity is complete for a considerable time, but this gradually wears off. Apparent or mild attacks in persons with partial immunity are believed to constitute an important source of infection.

Diagnosis.—Conditions which may simulate typhus are readily differentiated by laboratory methods. As has already been noted, the rashes of other members of the typhus group closely simulate that of exanthematic typhus and can be distinguished with difficulty. Stress is laid on the rarity of rash on the face and the fact that it does not come out in crops. The "tongue sign", first described by Okuniewski, is said to be very helpful in bed-side diagnosis. The patient is unable to protrude the tongue when ordered to do so; this is attributed to perivascular infiltration in the region of the nucleus of the hypoglossal nerve. The smell is characteristic of mouldy leather.

The Weil-Felix reaction in high dilution is diagnostic, but false positive reactions may occur in infective hepatitis, enteric, relapsing and undulant fevers. The titre of agglutination rapidly rises to 1 in 500 towards the end of the fever. During convalescence it remains about 1 in 50-1 in 100 for weeks and even months. A reliable strain of Proteus OX19, as from the

Oxford Standards Laboratory, should be employed.

Felix states that the type of titre curve is generally related to the clinical course: (a) moderately severe cases usually show high-titre reactions, (b) most severe cases usually give very low titres, and (c) the mildest cases have either very low or very high titres. In countries, where typhus is endemic, the titre of normal persons may be above 1:100. Subsequent to antityphus inoculation with rickettsiæ of the OX19 group (R. prowazeki and R. mooseri) agglutinins often appear, but titres are usually low. For carrying out the test, round-bottomed test-tubes, 2 by ½ in., are employed. Lower dilutions such as 1:25 and 1:50 should always be included. The tubes are incubated for two hours and are read after 22 hours at room temperature or, in the tropics, after the same time in the ice-chest. Readings with a lens at the end of two hours often assist in the early detection of high-titre reaction. This is often delayed and the maximum titre is usually reached in the third or fourth week.

The Weil-Felix test is no longer regarded as absolutely specific and most workers now use agglutination or complement-fixation tests with sus-

pensions of rickettsiæ.

A pseudo-positive Wassermann reaction is frequently given by the blood before the crisis. Fever is seen in male guinea-pigs in from six to ten days after intraperitoneal inoculation.

A complement-fixation reaction (Bengtson and Topping) appears to be reliable and may become a routine procedure when specific antigens become more generally available. Bengtson summarizes the results: of 216 sera giving a positive fixation for Rocky Mountain fever 92·1 per cent. had no cross fixation for endemic typhus antigen. Amongst 114 sera positive for endemic typhus 80 per cent. gave no cross fixation for Rocky Mountain fever. The long persistence of the complement-fixation reaction is a valuable feature as it facilitates retrospective diagnosis. (This statement applies to all members of the group.)

The rickettsiæ may be isolated from the blood at the height of the fever by inoculating 2-5 ml. intraperitoneally into male guinea-pigs and subsequently demonstrating rickettsiæ in the tunica vaginalis. Gear and Davis recently showed that South African gerbilles (*Tatera brantsi* and *T. afra*) are specially susceptible to typhus and die with heavy infection of the peritoneum. Exposure of these animals to X-rays definitely lowers

their resistance.

Skin biopsy for the identification of the rash has been proved particularly useful. Sections show the typical lesions resembling periarteritis nodosa. The petechiæ in the skin are due to thrombosis of the smaller vessels.

An intradermal test was introduced by Giroud (1938). The patient's serum is mixed with a definite quantity of rickettsiæ (emulsion of the tunica of a guinea-pig infected with the murine strain). The emulsion is injected into the skin on the inner surface of the thigh of a rabbit. Normal serum is used as a control. If the patient has, or has had typhus, no reaction appears, but in the controls it is marked.

Fleck (1947) has described the presence of a substance in the urine with the characters of a specific antigen of typhus rickettsiæ. It may appear in the first days and in an amount sufficient to give a precipitive reaction, and when injected into rabbits it gives rise to rickettsial and

OX19 agglutinins.

Differential diagnosis.—This has chiefly to be made from typhoid and is based upon the onset and course of the temperature curve and in the character of skin eruption. In typhus the temperature climbs quickly to a high level where it remains, in place of the slower escalator rise of typhoid fever. There is, moreover, a mild leucopenia in typhoid: a mild leucocytosis in typhus. The diffuse roseolar rash of paratyphoid (especially paratyphoid A) may sometimes resemble that of typhus, but nervous signs and symptoms are less severe, and roseola of palms of hands and roles of feet is not found in typhoid as in typhus.

The differential diagnosis from septic meningitis with skin eruptions may be difficult, and determinable only by examination of the cerebrospinal fluid and by the Weil-Felix reaction. Differential diagnosis has also to be made from measles, especially the malignant form, commonly observed in native races. In this case Koplik's spots are of assistance; moreover, in measles the rash is brighter, its edges are definitely more

marked and it is more profuse on the face. In the tropics, dengue, especially in the initial stages, may prove difficult, but the patient is never so ill, nor is suffusion of the face so marked. In severe smallpox the initial scarlatiniform rash may be confusing, but characteristic smallpox lesions are seen first on the face. Cerebro-spinal fever, purpura and relapsing fever have to be considered; the latter is frequently found in combination with typhus.

Treatment.—Special attention must be paid to details of nursing and to the hygiene of the mouth. The recumbent position is essential, and every precaution should be taken against bedsores. It is important that the patient should have as much fresh air as possible. It is customary to give stimulants, the most favoured being port wine—about eight ounces in twenty-four hours being sufficient.

Cardiac stimulants are indicated, such as tincture of digitalis, digitalin (gr. $\frac{1}{10}$) or digitaxin (digitaline crystallisée gr. 1/100). Strychnine gr. $\frac{1}{50}$ is also a good stimulant. Lumbar puncture should be employed to relieve delirium and other cerebral symptoms, for, as a rule, the cerebro-spinal fluid is under pressure. Plenty of fluids should be given and the diet should be as nutritious and easily digestible as possible.

Chloromycetin (chloramphenicol) was isolated by Ehrlich (1947) from a streptomyces in the soil near Caracas, Venezuela. It is a neutral compound which is stable in aqueous solution at pH 2-9. In distilled water it is unaffected by boiling for five hours. From laboratory studies by Ehrlich, Smadel and Jackson (1947) it seemed probable that it might prove effective in rickettsial diseases. It was tried out in treatment by Payne, Sharp and Knaudt (1948) in an epidemic in La Paz, Bolivia, late in 1947, in conditions of great severity at an altitude of 14,000 feet. Four of the cases presented signs of probable death, whilst five were moribund. The mortality rate was 28 per cent.

Chloromycetin 0·1 grm. per ml. is dissolved in propylene glycol, stored in rubber-capped vials containing 10 ml. Tablets for oral medication each contain 0·25 grm. chloromycetin. The results following slow intravenous injections were rapid. Within three hours headache and backache showed improvement and vision became normal. Oral dosage was equally effective, but required 8-12 hours longer for results to appear. The dosage was 1·5 grm. daily as a single oral dose for 2-8 days.

Dana and colleagues (1950) treated four cases, in all of which immediate response to chloromycetin was prompt and satisfactory. The dose varied from 3-4 grm. daily. A warning is given that diarrhea should be regarded as a toxic symptom and as a sign for cessation of the drug. Sanchez (1950) treated fourteen patients in Mexico with chloromycetin at the rate of 50 mgm. per kg. body weight. They became afebrile within four days, and in six relapses of short duration were encountered 48 hours after the temperature had fallen to normal. In Abyssinia d'Ignazio and Termine reported good results in the treatment of ten cases with chloromycetin. In order to ensure success they recommended continuing the treatment beyond the fall of temperature.

Later Smadel and colleagues used this antibiotic in Mexico with good effect by mouth. The initial dose was 40 mgm. per kg., followed by a daily

dose of 35 mgm. in divided doses, at intervals of two hours until improvement took place. Finally a daily dose of 20 mgm. per kg. should be given

until 14 days from the onset of typhus.

This drug has now been found to cause, in certain rare instances, bone marrow depression. Some eight cases of aplastic anæmia have been reported which have ended fatally. It has to be noted that substances which have in their structure a benzene ring with an attached amino- or nitro-group are likely to affect the bone marrow adversely, and chloramphenical has such a structure. Gill has described two cases of granulocytopenia in infants treated for acute salmonella infection, one after 12.3 grm. in twelve days and the other after 1.75 grm. in two. As this state develops so rapidly, any symptom suggesting affection of the blood-forming tissues, such as epistaxis, menorrhagia or sore throat should be a signal for discontinuing the drug.

Streptomycin is also of curative value. Smadel has shown that it inhibits rickettsize of typhus and Rocky Mountain fever, but not those of mite typhus. Nitroacridine and p-amino-benzoic acid possess a synergistic action when given together with streptomycin.

Aureomycin was given by Sanchez in Mexico to forty-two patients in divided doses by the mouth. The daily dose was 50-75 mgm, per kg. and treatment for 36 hours usually sufficed. The total duration of the fever averaged nine days. Nausea and vomiting often occurred, but did not necessitate interruption of the treatment. Those patients intolerant of aureomycin can be treated by chloromycetin. Stegert (1950) has shown experimentally that aureomycin in high concentration possesses a pronounced rickettsiacidal and antitoxic effect.

Prophylaxis.—The quarantine period of typhus is fifteen days. The main prophylactic measures consist almost exclusively in the destruction of lice. The body should be shaved, including the pubes and axillæ, the hair of the head cropped and a cresol bath taken.

A great advance has been made by the use of the insecticide, dichlordiphenyl trichlorethane (DDT), which is the active ingredient of louse

powder. (For further details, see p. 865.)

Prophylactic inoculation.—Several methods of active immunization against louse-borne typhus are in use in various parts of the world (see p. 256).

II. MURINE TYPHUS—FLEA TYPHUS

Synonym. Endemic typhus.

Geographical distribution and epidemiology.—This is worldwide, especially in Mexico, North America, India and Palestine. Typhus-infected rats have been found in the Mediterranean basin, Syria, Greece, Toulon, Malaya, North and West Africa and the Belgian Congo. The seasonal incidence remains constant; the majority of cases occur in summer and autumn. The incidence is twice as high in males as in females and the negro is less susceptible than the European. In West Africa this form has been found not uncommonly where it had not previously been

suspected, both in ports and in inland districts. The urban, or shop, typhus of Malaya (Lewthwaite) and India (Rice), which in both places is local in distribution, is also murine typhus. Murine typhus caused 5.338 cases in the Southern United States in 1944.

Ætiology.—Nicolle in Tunis and Zinsser in America took the view that murine typhus is the more primitive disease. It is clear that it is not spread from man to man, but from rat to man, the brown rat, Rattus norvegicus, being mainly concerned in temperate climates. They think that the infection may overflow to man, generally producing isolated cases without further man-to-man spread. According to an evolutionary point of view, this infection has undergone two mutations, by changing both its vertebrate and invertebrate host. In Mexico a type of typhus exists in rodents and man which may be regarded as intermediate between the murine and louseborne types. It is also true that many species of rickettsia are unstable. The more recent origin of epidemic typhus is indicated by the fact that R. prowazeki var. mooseri is harmless to the flea, while R. prowazeki causes death of the louse, to which it may be regarded as less adapted. It therefore appears probable that the endemic form may be easily converted into the epidemic, and that typhus infection may be maintained in the interepidemic period by rats. Thus, Raynal, Fournier and Velliot (1939) have adduced evidence in Shanghai that, under certain conditions, the rat rickettsia can be converted from the rat-flea-rat cycle into the man-louseman cycle. The armadillo and the field rat in S. America are susceptible to murine typhus (Varela and Mazzotti).

Weyer has shown that the mouse flea, Leptopsylla segnis, is susceptible to R. mooseri. Intracellular strains of rickettsia, virulent for mice, sometimes become extracellular and non-virulent after transfer through the

flea and further passage through lice.

Jadin has shown that the red fever of the Congo is endemic typhus and has isolated an orchitic strain from the brains of rats in Coquilhatville on the equator. The disease has a negligible death rate and the rash may be absent in 50 per cent.

On epidemiological grounds the association of endemic typhus with rats and grain stores was first suggested by Hone (1922) in Australia and subsequently by Maxcy (1926) in America; in 1931 proof was provided by Mooser, Dyer and his colleagues that the rat was the reservoir, and that rat fleas (Xenopsylla cheopis and X. astia) were carriers of the virus. Under normal conditions the infection is spread from rat to rat by the rat-louse (Polyplax spinulosa). Rats (R. norvegicus) collected from areas where numerous cases of endemic typhus had occurred, were chloroformed, then the fleas collected, emulsified and injected intraperitoneally into guinea-pigs. After four days' incubation period these reacted with fever and swelling of the testes (Neill-Mooser reaction).

In the same year Mooser, Castañeda and Zinsser in Mexico demonstrated endemic typhus virus by injecting guinea-pigs with a brain emulsion of rats caught in the endemic area. Dyer and his colleagues then demonstrated that X. cheopis became infected when fed upon infected rats and could convey

typhus to other rats.

Rickettsiæ of Murine Typhus in Mites.—Trombiculid mites, Schöngastia indica have been found naturally infected with murine typhus. The mites were taken from house rats (R. rattus diardi) and sewer rats (R. norvegicus). Emulsions of the mites were given intraperitoneally to mice which died in ten days. In guinea-pigs the strain had the microscopical characteristics of *R. mooseri* (Gispen, 1950).

Zinsser showed that the louse-borne, or human rickettsia and the rat rickettsia are two varieties of the same species, resembling each other in their antigenic properties, but not identical. Neither he nor Mooser could permanently transform the human virus into the rat virus. Thus, Zinsser and Castañeda found that formalin-killed murine typhus rickettsiæ conferred a higher degree of immunity against a homologous virus than against louse-borne typhus. The natural infection of a cat in a typhus hospital has been reported from Mexico.

General considerations.—It may well be asked why does not endemic typhus spread like plague, considering the close connection between rat and man? The answer is partly that X. cheopis in endemic typhus is not nearly so heavily infected as fleas in plague, or as lice in epidemic typhus. The difference in the vectors of epidemic and endemic typhus also accounts for the fact that the former is a disease of the winter months and of crowded insanitary peoples, whereas endemic typhus is a disease of warm weather, not associated with crowded humanity, but with the presence of rats. Other forms of typhus resembling murine typhus have been described from Australia, North and South Africa, whilst ship-fever of Toulon (fièvre nautique) is a local form; other varieties may be those forms of trench fever with a rash, and also the urban (W) form of tropical typhus described by Fletcher and his colleagues in Malaya with a tendency to spread amongst those engaged in handling grain.

Zinsser (1934) and Plotz (1949) thought that the disease described by Brill is recrudescence or relapse of epidemic typhus, but that endemic typhus in the Southern United States and Mexico is murine typhus. In the former the reservoir of the virus is man. These views have received support from the new complement-fixation technique with rickettsial

antigens.

Symptoms.—The symptoms resemble those of epidemic typhus, but are much milder in every respect. The mortality rate is very small (about 1.5 per cent).

Diagnosis and differential diagnosis are identical, but Bengtson and Topping in America showed that the agglutination test with rickettsial suspensions should clearly differentiate between murine typhus and Rocky Mountain fever. Complement fixation is more important than agglutination (Findlay and Elmes) (see p. 280).

Treatment with chloromycetin has been successful. Terramycin is effective. Aureomycin, 300 mgm. per kg. every three hours, is equally good (Sanchez).

Prophylaxis.—Reports from U.S.A. indicate that the incidence of murine typhus has been much reduced by applying 10 per cent. DDT to rat runs, burrows, and harbourages. Wiley has shown that a very considerable reduction in human cases could be recorded in dusted areas and that the numbers of *X. cheopis* had greatly diminished.

III. MITE TYPHUS—SCRUB TYPHUS

Synonyms.—Tsutsugamushi; Tropical typhus; Shimamushi; Japanese river fever; Kedani mite disease; "K form."

Definition.—A typhus disease with a high case-mortality rate, characterized by the presence on the skin of an *initial eschar*, supervening on the bite of a species of microtrombidium (the larval stage of *Trombicula*—a "velvet mite"). This is followed by an ulcer, lymphangitis, and a typhus-like rash.

Geographical distribution.—In Japan the disease is limited to areas near the banks of rivers on the west side of the main island and endemic in the Niigata province from May to October. The main rivers are Omono, Minase, Inaba, Mogami, Shinano, Aka and Nonuma. In Formosa and in the main island it is widely distributed, not only near river banks, but in cultivated fields, foothills and mountains (up to 6,500 ft.). The peak period is July to October. In the Pescadores Islands the houses are surrounded by the endemic area and all the inhabitants are exposed to infection. The disease is not contracted in the fields. peak period is April to November. In Borneo fatal cases have been reported in Brunei. In New Guinea the disease is widespread in New Britain and Papua. In Queensland it is known as Mosman, scrub or coastal fever and occurs in the eastern coastal area between Cooktown and Ingham. In Java cases are reported from Bandoeng: in Sumatra, in workers on tobacco estates in the north. In Malaya it is known to occur in Selangor, Pahang, Perak, Kedah and Negri-Sembilan. In French Indo-China it occurs in five divisions—Cambodia, Cochin-China, Annam, Laos and Tonking; in Burma-in Lower Burma, Rangoon, Syriam, Henzada, Prome, Toungoo, Bassein; also in Upper Burma. It also occurs in Siam, S. China, Java; in India, probably in the Simla Hills, Madras and Bombay. In Ceylon a few cases have been reported from the south-east part of the island.

Epidemiology.—The patchiness in distribution of trombiculid mites has been much commented upon. Mites seem to be limited to certain areas, particularly to tracts that were once under cultivation and are relapsing again into jungle. So accurately can this "typhus country" be defined that risk of infection can be foreseen fairly accurately from aerial photographs. Another striking feature is the wide variation, not only in infection rate, but also in mortality. There is no evidence of any difference in the virulence of local strains of R. tsutsugamushi, but considerable variation in the number of rickettsiæ that can be recovered from local trombiculids (Trombicula deliensis). The areas of greatest infectivity are on the mainland of New Guinea where mite-rat-mite passage is most easily effected. This was seen in South Bat Island (Lat. 2° 50' S., long. 146° 14' E.), in the Purdy Group, which is uninhabited except by pigs, flying foxes and a saturated population of rats infested with mites $(\tilde{T}.$ deliensis) and R. tsutsugamushi. Thereon 26, of a total of 41, sailors and soldiers in 1944 contracted scrub typhus within 46 days and 2 died. In Upper Burma the peak of the disease roughly corresponds with the beginning and end of the monsoon, when T. deliensis is most abundant, but it may be acquired in any month of the year. The main factors are exposure to mite infestation together with fluctuation of the mite population. An infected site remains hazardous for at least one year. Transovarian transmission of R. tsutsugamushi has been demonstrated to explain this feature. The mite is regarded as the vector as well as the reservoir of the infection. In this area the Yunnan buff-breasted rat (Rattus flavipectus yunnanensis) and the Assamese tree-shrew (Tupaia belangeri versuræ) were the only animals found naturally infected with R. tsutsugamushi (Mackie). In New Guinea and adjoining islands the types of infected localities were (1) open kunaigrass land, (2) abandoned banana and coconut gardens, (3) sparse, coarse growth of native vegetation, (4) areas on the edge of virgin forests.

The risk of contracting scrub typhus is great in the fringe of forest clearings in Malaya where the mite vectors are most common. Thus rubber plantations, overgrown by weeds, cleared jungle and abandoned vegetable gardens are dangerous. In these localities rickettsiae are found in pools of T. deliensis and T. akamushi collected from the jungle rats—

Rattus rattus argentiventer (Audy).

It is necessary to note that these larval mites do not digest blood, but only lymph and tissue fluids and they do not remain attached to their animal hosts for more than 3-4 days. The chief reservoirs of rickettsiae are the mites themselves. The vertebrate hosts serve only as transitory reservoirs (Philip).

Outside the endemic area it has been shown by Noury that the Moroccan rodent—Meriones shawi—is susceptible to intraperitoneal innoculation

with R. tsutsugamushi.

Ætiology.—The organism of "scrub typhus" is known as Rickettsia tsutsugamushi (orientalis). This organism is conveyed by the bite of an acarus (locally known as akamushi—the red insect), which is the larva of "velvet mites," either Trombicula akamushi (0.9 mm. in length) or T. deliensis. The adult stage is non-parasitic. This larva is popularly known as the kedani mite or "patau" (Figs. 827-828, p. 1010), the Japanese have always regarded it as the vector of this fever. (This mite somewhat resembles the harvest mite—the larva of T. autumnalis—and was formerly and incorrectly known as Microtrombidium or Leptotrombicula akamushi.) In Sumatra and Malaya, however, the vectors are larvæ of Trombicula deliensis and T. schüffneri respectively, which infest the undergrowth and long grass ("lalang") in clearings of the forest and there they are probably distributed by the crow pheasant (Centropus bengalensis javanicus). T. deliensis is pale ochre in colour: T. akamushi bright vermilion. It was thought, though not proved, that wild rats (R. rattus diardi), the rural rat (R. rattus jalorensis) and the house rat (R. concolor) could act as reservoirs of infection (Lewthwaite and Savoor, 1937). The larval trombicula occurs numerously on the ears of the field vole (Microtus montebelloi) and other rodents-Mus jerdoni, R. rattus refuscens, R. decumanus and R. agrarius. In Korea and Formosa it is disseminated by a small warbler (Acrocephalus stentorius orientalis), domestic fowls, the pheasant (Phasianus colchicus formosanus)

and a quail (Turnix javanica atrigularis). In the Mandated Territory of New Guinea, Gunther (1939) has always regarded T. minor as the probable vector, its principal hosts being the rat or bandicoot (Echymipera cockerelli), bush pig, fowl, turkey, cassuary and ground pigeon. In Papua the vector is probably T. hirsti or T. fletcheri (65-7 per cent. of mites on rats and bandicoots in New Guinea were found to be T. fletcheri from which R. tsutsugamushi was recovered).

The rickettsiæ have been found in the body-cavity of the adult mite, Trombicula akamushi, and in the salivary glands of the infective larval stage, but are now known to persist from one generation to the next—about 30 days. The infection may originally be contracted by the adult trombicula and thereby may be transmitted to the larva. The larval Trombicula requires one single meal of blood to complete its development. It attaches itself to vegetation, such as lalang grass or scrub, along the course of rivers. (R. tsutsugamushi remain viable in lice for about seven days, but cannot be conveyed, but in the flea, X. cheopis, it persists for eleven days so that the infection can be transmitted, under experimental conditions, by this ectoparasite.)

It is not possible at present to be precise in the classification of these larval mites. Entomologists who have studied this question are doubtful whether all criteria for differentiation are entirely trustworthy.

R. tsutsugamushi occurs in the blood in the incubation period of the disease. Monkeys can be easily infected with as small a quantity as 0-001 ml. The organisms are destroyed by heating at 55° C. for ten minutes.

Anigstein's claims to have cultivated the organism in broth have not been substantiated, but it may be maintained on yolk-sac embryo as well as in tissue culture made from the endothelium of Descemet's membrane of the rabbit eye with additions of normal aqueous humour and rabbit plasma.

Nagayo and others succeeded in transmitting the rickettsiæ by intraocular inoculation in guinea-pigs, also by intratesticular injection in rabbits, in which they produce a characteristic reaction. Cross immunity experiments have shown that no immunity exists between R. tsutsugamushi and R. prowazeki and that therefore these two members of the typhus group are distinct.

The literature of scrub typhus which has been extensively studied by British and American commissions during the recent war in the Far East is very extensive and it is difficult to summarize all their observations.

Pathology.—The lesion at the site of the infective mite bite undergoes coagulation necrosis and affects the epidermis, corium and surrounding tissues and is well delineated by a boundary line. This forms the eschar, or ulcer, which is usually, though not invariably, present. The spleen is enlarged, with tense capsule, soft, friable pulp, and focal necrosis; similar lesions are found in the enlarged and congested liver. The kidneys show pale swelling of cortex and a narrow zone of congestion. The lungs are congested; hypostatic bronchopneumonia is frequent, with pleural effusions. There is a general lymphadenitis; glands in the vicinity of the initial lesion are specially affected and may show central necrotic lesions. There is usually an effusion of clear fluid in the tunica vaginalis. There

is generalized ædema of varying degree and hæmorrhages into the body tissues.

Kouwenaar found that histologically the "typhus nodules" differ from those of the louse-borne form in that the chief change is the perivascular infiltration and that the intima of the blood vessels is secondarily involved.

Hicks considers the main changes are proliferation of the reticuloendothelium and infiltration of the interstitial tissue with large numbers of mononuclear cells. This process is most conspicuous in the heart and lungs, but also pronounced in the spleen, where angiitis is most prominent. The capillary endothelium throughout the body is swollen. Most of the lymphoid tissue of the spleen is replaced by this cell infiltration. The small vessels of the brain are shadowed by round cells and frequently small hæmorrhages are seen in the pons and mid-brain. According to McGovern the intima of the coronary vessels of the heart is especially affected and collections of round cells are found in the vasa vasorum.

Symptoms.—The person attacked by the mite does not usually notice the bite, but later feels a pricking sensation when he happens to touch the spot. Generally it crawls up and bites at first obstruction at bend of elbows. The mite, or mites, can easily be seen through a strong magnifying glass, with their heads and bodies buried in the skin, but only when they are carriers of the disease do any definite pathological changes take place round the lesions they inflict. After an incubation period of from four to ten days or longer, the disease begins with severe frontal and temporal headache, anorexia, chills alternating with flushes of heat. Presently the patient becomes conscious of pain and tenderness in the lymphatic glands of the groin, ampit, or neck. On inspection of the skin of the corresponding lymphatic area there is sometimes discovered usually about the genitals or armpits—a small (2-4 mm.), round, dark, tough, firmly adherent eschar with necrotic centre surrounded by a painless livid red areola of superficial congestion. This is the initial ulcer. Sometimes it may be merely a papule, which develops and disappears during the incubation period and therefore is seldom visible. Lewthwaite makes a point that an ulcer is not by any means invariable. Occasionally two or three such eschars are discovered. Although a line of tenderness may be traced from the sore to the swollen, hard, and sensitive glands, no welldefined cord of lymphangitis can be made out. The superficial lymphatic glands of the rest of the body, especially those on the side opposite to the glands primarily affected, are also, but more slightly, enlarged.

Clinical observers in Burma describe adenopathy as present in 90 per cent. The glands are most noticeably palpable in the posterior triangles of the neck. In a few cases this is so pronounced as to give a bull-neck appearance. The enlargement of the posterior occipital glands may be

the cause of occipital pain in association with neck rigidity.

Fever of a continued type now sets in, the thermometer mounting in the course of five or six days to 104° or 105° F, reaching its maximum at the 48 hours. The conjunctive become injected; the eyes are half-closed, watery and faintly glistening. Photophobia is invariable. At the same time, a considerable bronchitis gives rise to harassing cough. The pulse

is full and strong, ranging rather low—80 to 100—for the degree of fever present. The spleen is moderately but distinctly enlarged, and there is marked constipation.

About the sixth or seventh day the eruption of large dark-red papules appears. It is usually maculopapular, sometimes papular or macular. It lasts 3-4 days, mainly on the trunk, upper arms and thighs. It sometimes extends to the face, hands and feet.

During the height of the fever the patient is flushed and at night may be delirious. He complains incessantly, probably on account of a general hyperæsthesia of skin and muscles. Deafness is also a constant feature.

As the disease advances, the symptoms become more urgent; the conjunctivitis is intensified, the cough becomes incessant, the tongue dries, the lips crack and bleed, and there may be from time to time profuse perspiration. By the end of the second week-sooner or later according to the severity of the case—the fever begins to remit by lysis, the tongue to clean and, after a few days, temperature falls to normal and the patient speedily convalences. There is a well-marked leucopenia. When the leucocytes are increased some extraneous infection may be suspected. The red cells are normal, but there is a decrease in the coagulability of the blood. Bronchitis, diarrhea, or diuresis may occur during the decline of the fever. The circular, sharp-edged, deep ulcer left after the separation of the primary eschar—usually during the second week—now begins to heal, and the enlargement of the glands gradually to subside. The urine is albuminous and gives the diazo-reaction.

Such is the course of a moderately severe case. In some instances, however, the constitutional disturbance is very slight, although the primary eschar may be well marked and perhaps extensive. On the other hand, the fever may be much more violent, and complications, such as parotitis, melæna, coma, mania, cardiac failure, or ædema of the lungs may end in death. Similarly, the duration of the disease varies according to severity from one to four weeks, three weeks being about the average. Relapses do not occur. Menon and Ibbotson, in a clinical study of 100 cases in Burma, noted early sore throat in 56, eschar in 56 (2 and 3 eschars noted), conjunctival injection in 82, flushing of face in 65, lymphadenitis in 98, rash in 64, mental changes in 50-apathy and confusion, delirium of the "typhoid" state—diffuse bronchitis in 50. Cyanosis and hiccup are danger signals. Neck rigidity sometimes met is not associated with any change in the cerebro-spinal fluid. Bronchopneumonia or lobar pneumonia are terminal complications.

Dame (1946) found eye sequelæ in 98 per cent., especially subjective retinal findings consisting of enlargement of blind spots, contraction of visual fields, and scotomata. Minor non-specific involvement of the cochlear system of the ear was found in only 11 per cent. during

convalescence.

It has been stated that many persons bitten by infected mites complain of headache, oppression, general malaise and numbness at the site of the bite. These may subside in two or three days and may be caused by the secretions of the mite, but not by R. tsutsugamushi.

This view has gained some support from the fact that such phenomena

have been evoked by injecting an emulsion of freshly-macerated T. akamushi. Emulsions made with infected mites usually produce local necrosis.

Pregnant women contracting scrub typhus mostly abort and die.

According to Hatori, reinfection may occur.

The death-rate in Japan is high—from 25-80 per cent.—but much lower in Sumatra (0-15 per cent.). In Burna and New Guinea the mortality in British and American troops was from 10-15 per cent. In peace times the mortality varies from 0-6-35 per cent. (Philip).

Diagnosis.—The Weil-Felix reaction has proved of great value in diagnosis (see p. 223). The serum does not agglutinate suspensions of OX19, or OX2, but only OXK (Kingsbury strain) and this appears to be quite clear and definite. The main type of antigen is therefore OXK. Filtrates of OXK have been employed for an intradermal test (Kuroda). A positive reaction is said to supervene within a period of two hours, during the first few days of the illness only, but a negative reaction ensues after the sixth or seventh day.

United States medical authorities report that R. tsutsugamushi is readily isolated in the early stages by grinding up blood clot with normal saline and centrifuging at low speed; 0.3 ml. of the supernatant fluid is inoculated intraperitoneally into mice. Death occurs 10–16 days later, when rickettsiæ are demonstrated in peritoneal smears. Blake, Maxey and colleagues have found the Syrian hamster most suitable for passage of rickettsiæ after intraperitoneal inoculation. Wedd (1945) regards the speckling of the lymphocytes with azurophilic granules as diagnostic; the maximum counts are obtained during convalescence.

The limited geographical distribution, together with the initial necrotic ulcer and lymphadenitis, suggest the diagnosis. Plague and tularæmia may possibly be considered, but even if primary vesicles or ulcers occur in these diseases, the matting together and exquisite tenderness of the

lymphatic glands should be suggestive.

The differentiation of measles and dengue may also have to be considered **Treatment.**—On account of the helplessness of these patients and their inability to feed themselves expert nursing is vital. Nasal feeding is necessary in very severe cases (Willcox). The site of the bite should be treated by cauterization or extirpation. Common salt, 6–8 grm., should be given freely.

Lumbar puncture and drawing off fluid under pressure has had good results. As ædema is caused by fluid retention, regulation of fluid balance is important. Diuresis is usually noted about the fourteenth day. An adequate diet of 2,400 calories and 100 grm. of first-class protein is essential. Hiccups respond to CO₂ inhalations and oxygen, which is also necessary for cyanosis. As malaria is a common complication, atebrin in suppressive doses is advisable.

Chloromycetin (chloramphenicol) (see p. 231).—The action of this drug has been investigated in Malaya by Smadel, Lewthwaite and Savoor. Twenty-five patients were treated (1948) with twelve as controls.

Among those treated none has died and no complications have developed. The duration of the fever after the first dose averaged 31 hours and the whole febrile period 7.5 days. At first, the same large doses were given as in louse-borne typhus, but gradually dosage was reduced till

only 6 grm. was administered in 24 hours to the last seven patients, and the results were equally good. More recent reports by Smadel, Woodward and Lewthwaite in 69 cases corroborate the view that this drug exerts a powerful rickettsiastatic effect in nearly every case. The occurrence of relapses amongst patients who have received a course of treatment during the period of exposure to infection is probably due to the wearing off of the rickettsiastatic effect before the immunizing mechanism has become adequate to suppress those rickettsiæ which have survived. The leucopenia which is frequently encountered is to be ascribed to the action of the drug.

Aureomycin is probably equally effective, whilst terramycin in experimental infections is more active than either of the two antibiotics mentioned above.

Prophylaxis.—Dibutyl phthalate is lethal to mites, which are killed when walking on impregnated cloth. Two ounces of dibutyl phthalate (DBP) suffices to treat two sets of tropical uniform (blouse, trousers, underclothes, socks, etc.). Each man is issued with the fluid, which he smears on to his garments. The fingers are dipped into the fluid, the hands are then rubbed lightly together over the cloth, which is thus smeared with DBP. Experience indicates how many smears are needed to cover each garment efficiently, i.e., six smears per sock, thirty for trousers, etc. DBP resists up to eight washes in cold water, wading through rivers, heavy rain, etc. As a repellent, 5 per cent. emulsion of DBP in 2 per cent. soap emulsion is effective. Other prophylactic measures in endemic areas consist of cutting or burning the long kunai grass, or "lalang", as it is known in Malaya and subsequently spraying with oil. The local rats which act as vectors of the mites must be destroyed as much as possible and prevented from entering dwellings. (For prophylactic inoculation, see p. 255.) Snyder and Morton advocate a mixture of equal parts of benzyl benzoate and dibutylphthalate as most effective and more persistent than benzyl benzoate alone.

The spraying of dangerous areas with crude oil and the smearing of the legs of estate labourers with the same oil and the use of BHC (gammexane)

dust at the rate of 1 lb. per acre are advocated.

Chemoprophylaxis.—Smadel has advocated the use of chloromycetin as a prophylactic by giving 1.0 grm. daily by the mouth to volunteers. The drug was given during the days of exposure to risk and for 13 subsequent days. Between the twelfth and twenty-sixth days after first exposure 71 per cent. of untreated controls were attacked by scrub typhus. It was shown that in the treated group the disease was suppressed till at least eight days after the cessation of treatment.

The only significant difference between the attacks in these two groups was that no eschars occurred amongst the treated.

IV. TICK TYPHUS-ROCKY MOUNTAIN SPOTTED FEVER

Synonyms. Rocky Mountain Fever; Black Fever; Blue Disease. Definition.—A specific fever supervening on the bite of ticks—Dermacentor andersoni and D. variabilis—and resembling, symptomatically, louse-borne typhus. Other species of tick have also been incriminated.

Geographical distribution and epidemiology.—First described in 1896, it was originally thought to be confined to several of the Western States of the American Union: Idaho, Montana (Bitterroot Valley), Wyoming, Utah, Nevada, Oregon, Colorado, New Mexico and Washington States. It is now known to be divisible into two varieties, eastern and western. On the whole, the latter is thought to be the more deadly. The eastern form is gradually spreading and has been reported from 32 States, as well as from E. British Columbia, Alberta and Saskatchewan, the only U.S. States not infected being Maine, New Hampshire, Vermont, Connecticut, Wisconsin, Rhode Island, Michigan and Kansas.

Principally found in valleys and near the foothills of the mountains, it occurs in sharply-defined and limited areas. A new South American focus in Colombia was originally discovered by Patiño-Camargo (1935) on the Tobia river, a tributary of the Rio Negro, in a narrow valley of the Magdalena basin at an altitude from 2,300 to 4,100 feet, and a second, somewhat to the north-west, on the Villeta at 1,650-4,300 feet. The high death rate (95 per cent.) and the susceptibility of laboratory animals to inoculation made it probable that the rickettsia is identical with R. rickettsia. The tick vectors appear to be Anblyomma cajennense and Dermacentor nilens. The possibility of the identity with the tick-typhus of São Paulo (Brazil) has also to be considered, and it is closely related to fièvre boutonneuse. (Cf. evidence of Anigstein and Bader, infra.)

In the north-western regions of the United States the vector is Dernacentor andersoni which is prevalent from the middle of March to the middle of June, and in that region the majority of cases occur in April, May and June, occasionally in July and September. In eastern States the vector is D. variabilis which appears in March and December; most of the cases are reported in June, July and August. The infection conveyed by these ticks is therefore more common in women and children because dogs bring ticks into the houses.

It has become apparent that spotted fever is more widely distributed in America than was formerly considered probable, and that two principal types of the group in the Western Hemisphere can be distinguished—one transmitted by ticks of the genus *Dermacentor*, the other by *Amblyomma*; the latter covers the greater portion of Texas and a large part of South America.

Ætiology.—The organism is now known as Rickettsia rickettsii. There is conclusive evidence that R. rickettsii is introduced by the bite of the tick; only the adult normally attacks man (see p. 1015). Doctors are very susceptible, as is shown by the number of investigators who have perished from this infection. (Thus the late E. Brumpt became accidentally infected in his Paris laboratory, but recovered.)

The natural hosts of the wood tick, *D. andersoni*, are the Rocky Mountain goat, sheep, black bear, coyote, badger and lynx, but the larval stages develop principally on ground squirrels (*Citellus columbianus*) and the woodchuck (*Marmota flaviventris*). According to Bishopp and Smith, the immature stages of the dog tick (*D. variabilis*), are found on the meadow mouse (*Microtus pennsylvanicus*). The disease tends to occur in the spring months when these

ticks abound. These facts naturally gave rise to the idea that the animals acted as reservoirs of the disease.

The larva, nymph, adult male and female ticks have been proved efficient intermediaries for the parasite, whilst Dyer and others showed that the rickettsiæ are transmitted through the egg to the larva in a hereditary manner.

The proportion of infected ticks under natural conditions is quite small—only 1 in 296 in Ricketts' experience. He originally suggested from differences in the case mortality (in Montana 90 per cent.: in Idaho 5 per cent.) that two species of tick were capable of transmitting infection—D. andersoni and D. variabilis—and the suggestion proved correct. After feeding on infected blood there is a period of invasion which lasts 12 days, during which a multiplication of rickettsiæ takes place and they are converted into what is known as "tick virus."

The original suggestion by Ricketts that the reservoir of the rickettsia of this deadly disease was to be found in the ground squirrel, chipmunk and



Fig. 41.—Photomicrographs of Rickettsia rickettsii. × 2,000. (Dr. A. C. Coles.)

Rocky Mountain goat has not been confirmed. The recent work of Parker and colleagues, in Oklahoma, and of Anigstein and Bader in Texas (1943) afford grounds for believing that spotted fever intergrades between the South American form on the one hand and fièvre boutonneuse on the other. In an outbreak in Oklahoma the typhus infection was transmitted by nymphs of Amblyomma americanum. In infected guinea-pigs the rickettsiæ were identical with R. rickettsiä. The natural reservoir in this case was for the first time proved to be a rodent, the pocket gopher, (Geomys breviceps dutcheri). In Texas, evidence pointed to the dog as the natural reservoir, to the dog tick (Rhipicephalus sanguineus) as the vector, as well as A. americanum and probably also A. maculatum.

In human tissues Wolbach first observed minute bodies, staining with Giemsa, within the endothelium of blood vessels, in the substance of human and guinea-pig testes. The same forms were identified in the bodies, salivary glands and eggs of *Dermacentor*. Two morphological types were distinguished, one a lanceolate diplococcal form found in the circulating blood as well as in the endothelial cells and containing chromatin: the other rod-shaped and staining blue which proved to be the causative rickettsiæ. (Fig. 41.)

Pathology.—In addition to the skin rash, there is usually bronchopneumonic consolidation, or hypostatic congestion of the lungs, with subserous petechial hæmorrhages. Similar lesions are frequently seen in the brain. The myocardium is softened; the spleen enlarged and firm: the lymphatic glands generally enlarged; focal necrosis of the hepatic cells and congestion of the renal cortex are found. Constant lesions,

both in man and in artificially infected animals, are hæmorrhages into the genitalia and, quite often, gangrene of the prepuce and scrotum. Vascular nodules are a constant feature, but not so striking as in typhus, with perivascular mononuclear infiltration. Rickettsiæ are found in endothelial cells and in smooth muscle cells of the vessel walls.

Symptoms.—The incubation period is 3-7 days. The attack is ushered in by chills which are repeated with diminishing severity at irregular intervals throughout the attack. By the second day the temperature rises to 103° or 104° F. and by the fifth to 105° or 107° F. A typhus condition supervenes, with intense headache, photophobia, irritability and meningeal irritation. If the patient is to recover, the temperature begins to fall at the end of the second week and the fever usually subsides by lysis. There are intense muscular pains and very often an agenizing arthritis.



Fig. 42.—Rocky Mountain spotted fever on tenth day, showing confluent hæmorrhagic areas and a necrotic pressure area of the skin over the buttock. Texas outbreak conveyed by Amblyomma americanum. (By courtesy of Dr. L. Anigstein.)

The rash appears from the fourth to seventh day. It is first seen as small rose-coloured spots resembling measles, but soon becomes petechial, spreading so as to become confluent, especially on the more dependent parts, though it may occasionally be seen on the forehead. It is, on the whole, redder and more florid than that of louse-borne typhus. Later it spreads to palms, soles of feet and scalp. In some cases the spots remain discrete, brownish or purplish, giving a speckled appearance. Slight interior tinging of the skin and conjunctive is frequently observed. In some cases gangrenous patches of skin occur on the elbows, toes and lobes of the ears. During the third week desquamation sets in and the eruption gradually fades. (Fig. 42.)

eruption gradually fades. (Fig. 42.)

Constipation is the rule. The liver is usually enlarged; the spleen enlarged, firm and tender. Albuminuria is due to kidney involvement, and the highly-coloured, concentrated urine usually contains casts. Severe cases are characterized by cedema of the face and limbs. Nausea and vomiting set in about the beginning of the second week and in fatal

cases may persist throughout. Respiration is rapid, owing to respiratory catarrh. The pulse loses in volume as it increases in frequency. The erythrocyte count is little affected; the hæmoglobin content is slightly reduced and there is a mild leucocytosis of 12,000 to 13,000 per c.mm. There is a reduction in the blood-platelet count. Complications, such as gangrene of the tonsils, scrotum and prepuce, are common in the milder form. A high degree of immunity is produced and no instance is known of a second attack.

It is now recognized that there is little evidence for the view that eastern and western types can be distinguished. On the whole, however, in the west the rash tends to be more intense and widely distributed; the febrile period longer, headache, muscular pains and arthritis more severe, and the tendency to retinal hæmorrhages more pronounced. The percentage of children attacked is higher in the east than in the west.

Diagnosis.—The sudden onset, the intense muscular and joint pains, together with a negative Widal reaction, help to differentiate it from typhoid. The geographical distribution remains a most important factor in its separation from louse-borne typhus. The serological reactions belong to the indeterminate group. A feeble agglutination with *Proteus OX19* occurs and also with OX_2 and OXK. Guinea-pigs are easily infected and develop the Neill-Mooser reaction with swelling of the testes and scrotum. (For complement-fixation and agglutination of rickettsiæ which are more specific than the Weil-Felix, see p. 223.)

A differential table is given by Cumming and Millam between Rocky Mountain fever and endemic typhus (flea-typhus).

Rocky Mountain Fever.
Rural.
History of tick bite.
Children.
Several cases in the same family.
Fever up to 107° F.. lasts for weeks and ends by lysis.
Rush on wrists, then general, including palms of hands and soles of feet.
Mortality 25 per ceut. or over.

Endemic Typhus
Urhan.
Premises infested with rats and fleas.
Adults and middle-aged.
Sporadic.
Fever lower, ends by crisis in second week.
Rash first on trunk, flexor surface of limbs, rarely on face, palms or soles.
Mortality under 5 per cent.

Mortality varies considerably. In Montana it has been as high as 75-90 per cent. The percentage given by Topping (1941) was 19.4 for the western and 18.1 for the eastern form.

Treatment.—Chloromycetin (chloramphenicol) is as satisfactory in the fever as in other forms of typhus. There have been many reports to this effect. Pincoffs and colleagues first established its curative properties and found that convalescence was attained in what was formerly regarded as the most virulent of fatal diseases within three days. The adult dosage was 0.5 grm. every three hours until the rectal temperature registered below 100° C. for 24 hours.

Aureomycin is as good, if not better. Cooke advocated 1 grm. every six hours for two days. Harrell and colleagues give larger doses. The total daily dose varied from 3-6 grm. in divided doses every 4-6 hours.

They point out that care must be taken not to keep this drug in solution as it soon loses its activity. Ross and associates treated 13 patients varying in ages from sixteen months to fifty years. The results were remarkably good and vied with those obtained by Smadel in mite typhus. The average duration of fever after the first dose was $2\frac{1}{3}$ days and, even in two cases, where the treatment was not commenced till the eighth day the reponse was equally satisfactory. The dosage regime was three initial doses of 2–5 mgm. per kg., by the mouth, at intervals of one hour, then in the same doses every two hours till the temperature had remained normal for two days. The duration of treatment ranged from $4\frac{1}{2}$ –9 days. The average total amount was 9.5 grm. and the range lay between 2-3–16.3 grm.

Terramycin is probably equally effective, but there are only two reports up to date. Bauer, Powell and associates (1950) in seven cases gave as much as 3 grm. as a loading dose, followed by 1 grm. every eight hours. One case was refractory, but subsequently responded to chloromycetin.

Prophylaxis.—Attempts at prophylaxis are being carried out on the basis of the known methods of transmission. War is being waged on ground squirrels and woodchucks, the natural hosts of *D. andersoni*. Domestic stock, especially sheep and goats, are being systemically dipped with arsenicals, to prevent the spread of the tick. It must be borne in mind that *D. andersoni* does not infest human dwellings.

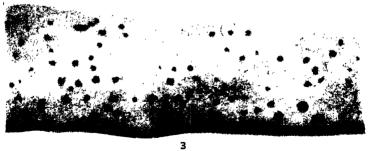
On the whole, the sheep is an uncongenial host; badly infected districts should be converted into sheep-runs. Workers in endemic areas should be clad in a one-piece costume, the trousers should be tucked inside woollen socks and the sleeves secured with a strap at the wrists. Tick bites should be immediately cauterized or, if possible, excised. D. variabilis is frequently brought into houses by house dogs, which may be freed from infection by the application of powdered derris root. Gammexane appears to be more lethal to ticks than DDT and can be used also as a repellent (see p. 866).

V. TICK TYPHUS (FIÈVRE BOUTONNEUSE) TICK-BITE FEVER

Synonyms. Marseilles fever; eruptive fever; fièvre exanthematique; escharo nodulaire; tick-bite fevers—South African, South American and Indian forms.

History and geographical distribution.—Frèvre boutonneuse was first described by Conor and Bruch in 1910 in Tunis, but is now known to occur throughout the Mediterranean littoral; also in Marseilles and many other districts in Southern France, as well as in Italy, Portugal, Spain, Greece, Roumania and the Crimea. Tick typhus also occurs in South Africa, East Africa and Abyssinia, West Africa, North African littoral; also in India, South-East Asia, Siberia and Queensland. This fever is transmitted by Rhipicephalus sanguineus in the Crimea and in other parts of S. Russia by Dermacentor nuttali, D. silvarum and Hæmaphysalis concinna. The West African form is related to the South African form (Findlay and Archer), but its vector has not yet been determined.





Rash of trypanosomiasis (T. gambiense.) (Dr. F. Murgatroyd).
 1(a).—Primary lesion, site of infecting testse bite on leg.
 Dengue rash (after Cleland, Bradley and MacDonald).
 Rash of fièvre boutonneuse on legs (after D. and J. Climer, 1933)

Distinctive features.—The distinctive features of this fever are that the rickettsia is transmitted by the common dog-tick, Rhipicephalus sanguineus (Durand, Conseil, Brumpt, 1980) and that the dog constitutes the reservoir of the virus, for these animals have been shown to be susceptible and their blood infective both for man and monkeys (Durand). The tick-transmitted virus (Rickettsia provazeki var. conori) passes hereditarily from one generation of tick to another without necessarily passing through a reservoir animal.

Another distinctive feature is the appearance of a primary sore, often in the axilla, at the site of the infecting tick-bite which, becoming gangrenous, is known as "tache noire", and varies in size from a pin's head to a pea, but is not usually painful. Lymphangitis subsequently occurs. These features are comparable with those of tick-bite fever of South Africa (Troup and Pijper, 1931) and of mite typhus. Gangrene of the scrotum has been described in an African by de Gac and Giroud.

At first French investigators hesitated to include it in the typhus group on account of discrepancies in the Weil-Felix reaction, but this has been cleared up. The Neill-Mooser reaction in guinea-pigs is positive, especially when an emulsion of infected ticks is injected (Caminopetros, 1982). No cross immunity exists between fièvre boutonneuse and endemic (fleaborne) typhus, and the latter appears to be definitely a local form of tick-borne typhus. In other respects it resembles Rocky Mountain spotted fever, but the rash (Plate VI, 3) tends to be papular as well as petechial. Unilateral orchitis is occasionally seen. There are therefore strong reasons for believing that it is closely related, in mode of transmission and ætiology, with the spotted fever groups of North America (p. 241).

VI. OTHER FORMS OF TICK TYPHUS

African form.—The tick-bite fever of South Africa, West Africa, East Africa, the Sudan, Eritrea, Somaliland, Mombasa and Abyssinia, originally described by McNaught in 1911, and again by Pijper and Dau in 1934, resembles fièvre boutonneuse, but is conveyed by larval ticks—Amblyomma hebræum, Rhipicephalus appendiculatus and Boophilus decoloratus (possibly also R. pulchellus and R. simus in Abyssinia, Eritrea, and Hæmaphysalis leachi in Tanganvika). Sporadic cases are reported from Johannesburg, Kenya and Abyssinia at 5,000 ft. These small ticks climb on to grass, attaching themselves to man and animals and, being veld dwellers, are not found in houses or on domestic animals. The disease in this respect resembles Rocky Mountain fever. In nature, infection is conveyed by tick-bite, and rickettsiæ can be demonstrated in the Malphigian tubules of the ticks; an emulsion produces the disease in animals and a slight Neill-Mooser reaction in guinea-pigs. The serum reactions in man are not quite clearly cut. In most cases Proteus OXK is agglutinated in a higher titre than OX19. Pijper and Crocker (1938) have shown that the rickettsia of this tick typhus does not immunize against the louse-borne or murine forms.

Two forms of South African "tick-bite fever" are described: mild, or abortive, and fully developed. In the first the only symptom may be the primary sore, accompanied by adenitis and lymphangitis at the site of

the bite. In the fully-developed form, in addition to the primary manifestations, the fever lasts ten days, with severe headache, stiffness of neck, conjunctivitis and petechial rash on the fifth day. It is apt to be confused with cerebro-spinal meningitis, measles and typhoid fever.

Gear and Douthwaite regard the dog as the reservoir of infection in South Africa, especially in the Cape Province, where it is suggested that the local dog-tick *Hamaphysalis leachi* may transmit the infection.

South American form.—South American tick typhus, also sometimes known as "Tabardillo," or "burning fever," is a form of tick typhus common in Minas Geraes, Brazil (Magalhaes, 1940); it resembles fièvre boutonneuse and may be the analogue of Rocky Mountain fever farther north, as Parker, Davis and Dyer have shown that there is cross-immunity. It is possibly the same as the rural disease which has occurred in Colombia and Texas (see p. 242) and Montiero succeeded in transmitting the rickettsize through the tick Amblyonuma cajenneuse, producing intraocular lesions in guinea-pigs and monkeys by the injection of infected human blood. Rickettsize were demonstrated in the endothelial cells of Descemet's membrane.

The mortality is said to be high—about 80 per cent. Ambulatory forms are recognized. There is usually a local lesion and adenitis. The grave forms are associated with sudden onset, severe pains, vomiting and delirium. Magalhæs found a leucocytosis up to 59,800 per c.uum. in 74 per cent. of the cases; leucopenia is exceptional; in severe attacks the blood urea is as high as 205 ngm. per cent. The urine is scanty, urea content diminished and there is chloride retention in the majority of cases. The Weil-Felix reaction is not clear-cut (Fialho, 1932); agglutination with OX19, OX2 and OXK is found in low dilutions. Dias (1938) stated that the natural reservoirs are the opossum, domestic and wild dog (Cerdocyon thous), the wild rabbit (Sylvilagus brasiliensis) and the agouti (Dasyprocta). The tick vectors are several species of Amblyomma:—A. cajennense, A. striatum, A. brasiliense; the former especially, according to Dias, is commonly parasitic on the domestic dogs.

Indian form.—McKechnie (1911) found a mild sporadic form of typhus in the Kumaon Hills on the North-West Frontier districts of India, and Megaw (1916) suffered from such an attack which he attributed to the bite of a tick. Other cases have been reported by Stott (1935) from Lucknow and by Webster (1939) from the Simla hills, but there is also evidence that mite-borne typhus exists in parts of India.

VII. TRENCH FEVER¹ (FIVE-DAY FEVER, VOLHYNIAN FEVER)

Definition.—This curious fever played a prominent part in the medical history of the 1914–1918 war on the Western (French) front, especially amongst the troops and to a lesser extent amongst civilians. It also occurred in Poland, Russia, Northern Italy and Macedonia. Until 1941 it was not encountered after 1918 under natural conditions, though a fever resembling it appeared amongst laboratory workers in Weigl's laboratory, who had been feeding lice on their bodies (Herzig, 1989). The Germans encountered it once again on the Russian front in 1942.

¹ Trenchfever, Q fever and rickettsialpox are quite distinct really from the true members of the typhus group and the rickettsize are not antigenically related. They are therefore placed together.

Its association with rickettsiæ and its transmission through the louse are claims for its inclusion within the typhus group. Trench fever is characterized by an initial febrile period, a tendency to relapse, periodic pyrexia and hyperæsthesia of the shins.

Geographical distribution.—Possibly it may be identical with "Volhynian fever," known to Polish physicians for some years before 1914. It was first recognized as a specific entity during 1915, when it appeared in all the European theatres of war, and no less than 800,000 cases were recognized in the Allied Forces in France, with isolated instances notified from Italy, Greece, Egypt, Iraq and Russia.

Lice in Tunis are infected with rickettsiæ which when inoculated into man produce symptoms similar to those of trench fever.

Epidemiology.—Trench fever is transmitted by lice alone, and the blood of the patient remains infective to these insects for long periods. These factors suggest that the disease might have a wider distribution than was at first suspected, but this has not been borne out. Trench fever cases have a group distribution consistent with the migrating habits of the louse which tends to leave the fevered human host.

Ætiology and transmission.—Rickettsia quintana is transmitted in the excreta of the louse and multiplies in the cuticular margin of the epithelium of the midgut of that insect. The virus exists in the blood of man and can be transmitted by inoculation of blood, or plasma. It has also been found in urine, sometimes in saliva, but never in fæces. It is killed in one hour at 70° C.

The infection is conveyed by lice fed on trench fever patients, the infected excreta being inoculated by scarification; lice crushed and rubbed into the scarified skin also convey the disease. A cycle of development of rickettsiæ takes place in the louse and occupies five days, during which time the insect is not infectious. Lice remain infective for at least twenty-five days and the rickettsia is not hereditarily transmitted through the egg. The infection persists for a long time in the blood of the patient and can be conveyed eleven weeks after an attack. Neither high nor low temperatures appear to influence the developmental cycle of this rickettsia in the louse.

Mooser and associates produced lesions on the skins of rabbits by inoculation with suspensions of lice infected with R. quintana. Hyperæmic papules with central necrosis were produced within four days. Subsequently intracutaneous inoculation into the skin of susceptible volunteers caused an attack of trench fever in which irregular paroxysms occurred between the eighth and twenty-third days. On the tenth day a small pale red papule was seen at the site of inoculation. Similar inoculation into a subject who had undergone an experimental trench fever attack three years previously resulted in the appearance of a small papule which did not become necrotic and disappeared quickly.

Symptoms.—Several types of fever were originally described, but relapsing pyrexia is usually present. Paroxysms of fever, lasting one to two days, recur at intervals of four to six days. An undulating type,

with recurring waves of four to ten days, has also been described. The incubation period is about two to three weeks; by scarification eight days; by transference of lice fourteen to thirty-eight days. The onset is usually sudden. There are headache, giddiness, pains in back and legs, often profuse sweats, flushing of face and injection of conjunctive. The spleen is enlarged in one-third of cases. There is no marked exanthem, as in typhus, but a pale pink erythematous or roseolar eruption which disappears on pressure has been described in one-third of the cases, usually coinciding with a relapse.

Bernsdorf (1944) in the German forces on the Russian front described the following types: (1) Classical five-day type—uncommon, (2) irregular recurring type with paroxysms every ten days, (3) undulant type with irregular recurrent waves of fever, (4) atypical forms, (5) afebrile types, (6) vegetative-dystonic types with vasomotor disorders, abdominal pain

and urticaria.

Tenderness and pains in the shins are characteristic, often very acute indeed, but usually not present in the early stages. Severe pains are also felt in knees and thighs, sometimes in the gastrocnemii. Held (1945) thinks that the pain is produced by nodular or cord-like bodies which are disclosed by careful examination of the scalp and other parts of the body which are tender to the touch. There is nothing characteristic in the blood, save a moderate leucocytosis of 10,000–14,000 per c.mm. Sequelæ are few and mild, such as slight febrile attacks, myalgia, tachycardia and debility.

The disease is never fatal, but shin pains often persist after subsidence of other symptoms. Complete recovery is the rule.

Treatment.—The patient should be confined to bed for at least three weeks. Amidopyrine, 1-2 grm. daily, is the only drug which has been found to have any effect upon the pyrexia or shin pains. Omnadin, a mixture of albuminous bodies, is recommended for relief of pain. The dose is 4 ml. daily for three days, then 2-4 ml. on alternate days up to a total of ten injections. The painful spots are best treated by massage. X-ray treatment is advocated by Hesse and Kremser in doses of 110 r (100 k.v.; 6 m.a.; 3-mm. aluminium filter; tube distance 40 cm.). For the head region 180 k.v. and a copper filter of 0.5 mm. is used. Applications are made to the lumbar and lower dorsal region of the spine. The shin bones, knee and ankle joints are also irradiated and for severe headaches the temporal region.

VIII. "Q FEVER" (QUERY¹ FEVER)

History.—A new fever was noted in 1985 in meat-workers in Brisbane, Queensland, by Burnet and Freeman, and since then many cases have been described. By 1989 it had been realized by Dyer and his collaborators that the organism—Rickettsia burneti—is the same as that described in America as R. diaporica, which is spread by the ticks, Dermacentor andersoni and Ornithodorus turicata, in Wyoming and the Western United States. This organism has recently been renamed Coxiella burneti, Parker, a terminology which has been accepted.

¹ Not Queensland Fever as has been erroneously stated.

Geographical distribution and epidemiology.—Q fever occurs in Queensland and is widespread in America, outbreaks having occurred in Montana and in Texas as well as in Panama. There is now evidence that it has a wider geographical distribution for during the recent war it affected British, American and New Zealand troops in Greece and Italy. In 1947 four familial outbreaks were observed in Switzerland. There is evidence that the disease is present in Morocco (Blanc) reaching to the south, including Casablanca and Agadir also in Algeria, Corsica, France, Iraq and now it appears to have a world-wide distribution and cases have recently been reported in Great Britain (Stoker) and Switzerland. In 1948 outbreaks were reported in Turkey and S. Germany. There is no obvious relationship to season. Before the war of 1939-45 most cases had been noted in meat-workers or dairy farmers. The outbreaks in European countries appear to be spread by droplet infection and numerous laboratory outbreaks have been described (Oliphant and Parker; Nauck and Wever) and ascribed to inhalation of infected dust. An outbreak in the Belgian Congo with 40 deaths and the isolation of C. burneti from body lice is recorded by Jadin and Giroud.

Pazzin has described an outbreak in a Turkish village for which inhalation of infected dust from wool was held responsible. Klopstock reported a similar outbreak in Israel. Gsell first established the occurrence of Q fever in Switzerland in men engaged in unpacking cases of heavy goods from America. An outbreak in Chicago slaughter houses was ascribed to handling freshly-killed animals. Q fever-in California occurs in cattle and in people associated with them, whilst C. burneti has been found in fresh milk in Texas. Irons and colleagues have shown that 5 per cent. of slaughtermen harbour complement-fixing antibodies for Q fever and these are also present in sheep and goats. On the other hand there are many recent reports of tick transmission in S. Europe and N. Africa and in U.S.A.

De Prada isolated *C. burneti* from the blood of man as well as from *Hyalomma savignyi* (*H. ægyptium*) in Salamanca, Spain; Sussman from *Rhipicephalus sanguineus* collected from a dog in Phænix, Arizona; Jellison from an argasid tick, *Otobius megnini*, in California; Blanc and Bruneau from *Hyalomma mauritanicum* in Algeria and from the merion

(gerbille) and its tick, H. excavatum lusitanicum in Morocco.

In England Stoker (1949) found serological evidence of Q fever in Britain, whilst C. burneti was isolated by MacCallum and colleagues during an outbreak at the Royal Cancer Hospital, London. C. burneti was present in milk. The clinical features were described by Marmion. A larger outbreak was reported in a Canterbury school by Harvey, others in 1951, and a third in S. Kent (Stoker and Thompson, 1953). Examination of milk from 103 herds in Kent showed that 8.2 per cent. were excreting C. burneti. Q fever is unevenly distributed in England. The highest incidence is in the S.E. No reservoir of Q fever other than cattle has been found in Britain.

Weyer and Nauck have established that *C. burneti* can be maintained in meal worms, but the abundant growth kills them in one week.

Ætiology.—Coxiella (R.) burneti is morphologically similar to C. (R.) diaporica (Fig. 43) and produces characteristic pathological effects in

monkeys, mice and guinea-pigs. There is a well-defined febrile reaction, during which time the blood is infective for guinea-pigs. Mice inoculated intraperitoneally show enlargement of liver and spleen with characteristic histological changes. In sections and smears of infected mouse liver and spleen large numbers of rickettsiæ occur in relatively large intracytoplasmic colonies (Fig. 43). It is the smallest of all the rickettsiæ and is filterable. In experimental animals it has to be distinguished from Goennert's virus disease of mouse lung.



Fig. 43. Coxiella burneti (diaporica). American Q Fever.
(Wyoming, U.S.A.)

(Slide prepared from peritoneal scrapings of infected guinea-pig by
L. Anigstein, Galveston, Texas.) Giemsa. × 1500.

C. burneti can be cultivated on minced chicken embryo reaching its maximum growth during the second week. When eight or nine-day embryos are inoculated, in membranes removed after six days and incubated at 34° C, numerous rickettsiæ are visible. After numerous passages on egg-membrane the American strain shows no reduction in virulence for guinea-pigs. Cox and Bell similarly cultivated the American strain in chicken embryo, in flasks containing yolk sac tissue suspensions

and filtered human ascitic fluid, in which it develops more profusely than does the Australian coxiella.

The natural reservoir in Queensland is the bandicoot (Isoodon torosus), which is very susceptible to experimental infection. 1 Smith and Derrick (1940) isolated the rickettsia from a tick, Hæmaphysalis humerosa, which is normally an ectoparasite of the bandicoot and opossum. More recently (1942), Derrick and Smith found that cattle may play an important part in transmission, and that human disease may result from direct infection from the body tissues of infected cattle. or further indirect infection from them by the body tissues of ticks, especially Boophilus annulatus microphis.

Since 1938 it has been ascertained by Davis, Cox, Dyer and others that the organism, R. diaporica, which was first isolated from the tick, Ornithodorus turicata, is identical with R. burneti and should be known as C. burneti var. americana. Davis (1940) showed that it may persist in the tissues of this tick for three years. Since then, outbreaks of Q fever have occurred (Hornibrook and Nelson), and this organism has been recognized in ticks, principally Dermacentor andersoni, in Montana, Wyoming, Oregon and California. Similarly, Smith and Derrick ascertained that C. burneti exists as a natural infection in Hæmaphysalis humerosa in Australia. The range of susceptible hosts is the same in both varieties, but the American (Montana) strain appears to be more virulent except for mice. Dermacentor occidentalis and Amblyomma americanum also harbour the rickettsiæ. There is some evidence that congenital transmission may take place in the tick.

In Morocco C. burneti has been isolated from the spleen of infected merions (Meriones shawi) as well as from ticks, Hyalomma savignyi and H. excavatum, var. lusitanicum, found living in the burrows of this North African rodent. addition goats carry infected ticks. These animals on inoculation with C. burneti exhibit a febrile reaction during which rickettsize circulate in the blood. H. dromedarii from the camel is also infected and the rickettsiæ pass into the eggs of the tick. In addition to sheep and goats, camels and cows react with fever and produce agglutinins to C. burneti. Wild rodents, including rats and

jerboas, are susceptible.

Burnet and Freeman confirmed the findings of Dyer that the C. burneti of Australia and of America are identical. Both Montana and Australian Q strains are agglutinated to the same titre by sera from a number of animals experimentally infected with one or other strain. Sera from man and animals infected with other rickettsial diseases do not agglutinate C. burneti. Guinea-pigs protected against Rocky Mountain fever are not immune to Q fever, but protection against Q fever is active against the virus recovered from wood ticks (D. andersoni) in Montana and the serum of patients recovered from Q fever protects against both Australian and American strains. As with other rickettsial infections, mixtures of virus and immune serum in suitable proportions may be injected into animals without febrile response, but in all instances the subsequent complete immunity of the animal indicates that actual infection has indeed taken place.

C. burneti is present in the blood of man during the fever period only, but may be found in the urine during the later stages. It is also present in the pulmonary cases in the sputum and can be conveyed to mice and guinea-pigs by this means.

Agglutination reaction of rickettsial suspensions by human, monkey and guinea-pig sera occurs and is specific, so that agglutinins are present in the serum of man and animals for several months after an attack. There is no crossimmunity between this disease, typhus or Rocky Mountain fever (Pinkerton, 1940). The disease produced in the guinea-pig is mild and mortality is nil, but when the animal is killed the spleen is found enlarged and contains the

¹ This animal is a marsupial and is quite distinct from the bandicoot rat (Nesokia bandicota).

organisms. One attack in the guinea-pig confers immunity and this has proved a method for diagnosis. These animals are readily infected by fæces of the tick, Ornilhodorus turicata.

Pathology.—The pathology has been described by Whittick (1950). The lung resembles lobar pneumonia. Coccoid and bacilliform rickettsiæ can be clearly demonstrated in the mononuclear cells and degenerated macrophages when stained with Giemsa; also in the testes and in the neuroglia cells of the brain.

Symptoms.—This fever is known in America as "Nine-mile fever." The onset in man is acute and sudden. The course and duration vary considerably. It is very infectious. In Europe and America it is probably commonly conveyed by dust, not by droplet contamination. Milk from cattle and goats may be a vehicle. Sometimes there is a rapid defervescence after six to nine days; sometimes the course is protracted to the third, or even to the fourth week and the temperature falls by lysis. There is no rash as in other forms of rickettsiasis. The outstanding symptom is headache which may be extremely severe and persistent, while the pulse-rate is slow. The disease is comparatively mild and there have been no fatalities.

Hornibrook and Nelson reported an outbreak in 15 persons amongst 153 employed in one building in North America. No valid evidence was obtained in this instance that any arthropod was concerned with the outbreak, or in the transmission of the disease. It is very suggestive that central pneumonia, or pneumonitis, has been observed and bronchopneumonic signs are present in half the cases. The disease is readily acquired in the laboratory and numerous cases have been reported. Encephalitis as a sequel to Q fever has been reported (Wegmann).

Findlay found that intranasal instillation of *C. burneti* (American and Australian strains) in mice causes interstitial pneumonia. These lesions are similar in character to those produced by similar applications of the rickettsiæ of louse-borne and murine typhus.

Diagnosis.—An agglutination test with suspensions of rickettsiae grown on egg-sac is now employed and is highly specific. Agglutinins are present in the serum for several months after an attack. A complement-fixation test was employed by Bengtson. Diagnosis can also be made by isolation of the organism in mice and guinea-pigs, or by feeding ticks on the patient and by subsequent transmission to mice. Neither the sera of patients, nor that of infected monkeys and rabbits, agglutinates *Proteus OX19*, OX2, or OXK. Radiographs of the lungs show evanescent diffuse opacities in the central portion and hilum. Derlinger described segmented or lobar consolidation in chest skiagrams in the great majority of cases; nevertheless recovery is rapid and complete.

Differential Diagnosis.—The fever has to be differentiated from atypical pneumonia, influenza, central pneumonia and psittacosis. The presence of "cold agglutinins" may assist in diagnosis from virus pneumonia.

Treatment.—The majority of modern antibiotics are curative in Q fever. At first streptomycin was used as Huebner and colleagues had found it

especially effective in treatment of guinea-pigs infected with *C. burneti*. Chloromycetin by the mouth has been generally acknowledged as specific, but recently *terramycin* is rated as even better.

Prophylaxis.—Burnet and Freeman found that the virus, when mixed with immune serum or treated with lauryl sulphate, confers immunity after inoculation, and so also do suspensions of rickettsiæ killed by heat or treated with formalin. The appearance of fever in abattoir workers has now been explained as due to handling meat of infected cattle. It is therefore obviously important that all meat workers should be protected by prophylactic inoculation. In the European outbreaks prevention is difficult because there is no contact infection, but it arises from a common source, such as dust. The rickettsiæ have been found in the fæces of ticks and other insects.

IX. RICKETTSIALPOX (VESICULAR RICKETTSIASIS)

This curious rickettsiasis was described by Huebner and Armstone in 1946 in inmates of an apartment house in New York with a pox-like rash. Within the next three years nearly 500 cases had been reported—all in New York City. The initial lesion resembles that of mite typhus and the rash is similar to that of other members of this group, except that vesicles occur. A case has been reported from French Equatorial Africa (de Gac and Giroud, 1951).

The incubation period is about seven days and the temperature rises on the tenth after infection. The lesion starts as a small erythematous patch and soon a vesicle appears with centre developing into an eschar with enlargement of the corresponding lymph glands. Malaise and headache are invariably present. Fever lasts one to seven days. The rash appears on the second day in the form of discrete erythematous, maculo-papular spots, 2–10 mm. in diameter, all over the body.

At a later stage the vesicles are replaced by blackish crusts which drop

off leaving pigmented spots. This disease has no mortality.

The causal agent is *Rickettsia akari* which is transmitted by the mousemite, *Allodermanyssus sanguineus* (Hirst). *Bdellonyssus bacoti*, another murine parasite, is also capable of transmission under laboratory conditions. The rickettsia are extracellular, intracytoplasmic and intranuclear.

The domestic mouse is undoubtedly the reservoir and they have been found carrying infected mites, whilst they themselves have been proved to be immune. The Weil-Felix reaction is negative, but complement fixation tests, with ether-extracted soluble antigens, are reliable, giving a rising titre response. Reactions with Rocky Mountain fever antigens are positive also. (A good general account of this rickettsiasis has been written by Greenberg and Pellitteri, 1952.)

Treatment with aureomycin, 2-4 grm. daily, has been successful, whilst terramycin is also effective.

PROPHYLACTIC INOCULATION OF THE TYPHUS GROUP OF FEVERS

A vaccine, to be of real value in the control of rickettsial infection, must produce a high degree of immunity which lasts for a considerable time; must not evoke dangerous reactions; and must be easily produced and easily administered.

Killed louse-borne typhus vaccine.—The earliest and most widely used method was that of Weigl. This vaccine is prepared from the intestinal contents of lice injected per rectum with suspensions of living Rickettsia prowazeki. After an interval the lice are killed and the intestines removed and ground up with dilute formol-saline. This method was employed in Poland and in Germany before the second world war. Considerable numbers of lice—between 200 and 300—are required to immunize a single individual, and the cost is great. Przesmycki introduced solutions of aureomycin into laboratory bred lice in doses of 0.01 per cent., at intervals of 24–48 hours; growth of rickettsiæ was inhibited.

Killed tick-typhus vaccine.—A method in which the tissues of infected Dermacentor andersoni are used has been employed by Spencer and Parker since 1925 in vaccination against Rocky Mountain spotted fever; 150,000 people had been inoculated by 1935, and Parker (1941) stated that amongst persons infected within one year the mortality was only 8·11 per cent. as compared with 82·35 per cent. amongst unvaccinated controls. Similarly, Monteiro (1938) has used the tissues of infected Amblyomma cajennesse as a vaccine against São Paulo typhus.

Other cultural methods.—The chief difficulty lies in obtaining rickettsiæ in large enough numbers. Numerous methods have been used: e.g., rickettsiæ have been grown in serum with Tyrode's fluid containing chick embryo tissues, but the growth, which is at first luxuriant, cannot be maintained. Cox devised a method of injecting rickettsia (from typhus, Rocky Mountain spotted fever, fièvre boutonneuse and Q fever) into the yolk sac of the developing chick embryo, which yields a rich growth. Formolized or carbolized suspensions obtained by this method have been used in Spain and extensively during the civil war. By this method one dozen eggs yield 100 ml. of vaccine, enough for about thirty people.

Cox's vaccine can be produced in large quantities. The virus is grown in developing fowl embryo and is transferred to other fertile eggs by 0.5 ml. of 5-10 per cent. suspensions of yolk sac in 50-50 mixture of sterile beef infusion broth, or by using an equal quantity of undiluted yolk fluid. The latter method is preferred for the preparation of vaccines. The maximum multiplication is not usually obtained before 4-6 passages. Formolized suspensions of the rickettsiæ are then prepared, and have been found to be stable on storage. The vaccine is injected three times (0.5 ml. once and 1 ml. twice) at five-day intervals.

The customary methods so far employed as a means of testing the efficacy of typhus vaccines are active immunization of guinea-pigs, agglutination tests for *Proteus OX*19, and neutralization of antibodies in

the serum of inoculated subjects.

The protection afforded seems to be only partial. Van den Ende and others (1943) published a report of an outbreak of murine typhus in twelve laboratory workers who had been immunized previously with Cox's vaccine. The infection was contracted by the respiratory route. The disease was moderately severe in three cases; mild in others.

Suspensions of rickettsiæ from tissues.—A different method consists of obtaining a rich suspension of rickettsiæ from the lungs of animals infected by the intranasal technique. This consists of setting up a rickettsial pneumonia in mice, in rabbits or, recently in South Africa, in gerbilles, removing the lungs and obtaining by centrifugalization a rich emulsion which is then treated with formalin or phenol. No reactions are caused by the injections, of which it is necessary to administer four or five at intervals of five days. A good immunity is said to be produced against louse-borne typhus, but only partial against the murine form. Castañeda (1941) proposed to use a lung vaccine prepared from rats in a similar manner, and to employ both types of rickettsia in the vaccine.

Fulton and Joyner (1945) during the recent war produced a vaccine by cultivation of R. tsutsugamushi in the lungs of the cotton rat (Sigmodon hispidus) by the intranasal method of Castañeda. In order to avoid infection of laboratory technicians all intranasal inoculations and grinding of infectious tissues were carried out inside the special box described by Van den Ende (1943). The Karp strain of Topping in lyophil dried volk sac was employed and it was recovered by injecting reconstituted material into the peritoneal cavity of mice. The viscous peritoneal exudate was used for injecting mice intranasally. In order to avoid contamination each mouse received intraperitoneally 15 mgm. sulphathiazole suspended in 0.1 ml. of 5 per cent. gum acacia saline. The lungs were harvested by grinding in a mortar with glass powder and suspending in 10 ml. of 10 per cent. horse serum broth. After centrifugation the deposit was discarded and the supernatant fluid stored in ampoules at -77° C. The lungadapted Karp strain was then passed intranasally to cotton rats which are most susceptible. They received intranasally 0.6 ml. of mouse-lung suspension, dying on fourth to fifth day. The rickettsize content of the cotton-rat lung is three times that of the mouse lung. The vaccine finally prepared appeared to be poor in protecting the mouse against scrub typhus compared with epidemic typhus vaccine. In man the vaccine does not give rise to any untoward reactions and it is suggested that three doses of 1 ml. subcutaneously at weekly intervals would be suitable and a booster of 1 ml. every three months.

Three cases of accidental infection occurred amongst 60 at risk. All had been inoculated previously and made uneventful recoveries. Two had previously suffered from murine typhus two years earlier. Tests in the field by Walker, Card and J. M. Walker (1947) with the vaccine in 1 ml. doses on three occasions at weekly intervals, showed some protection against the incidence, but that it had no effect upon the classical cases of scrub typhus.

General considerations.—Felix has emphasized that immunization against the typhus group is still in the experimental stage; one of the chief difficulties is to maintain the labile rickettsial antigen in cultures. The best method of killing and preserving the vaccines has yet to be found. At present phenol and formalin are employed, and it is probable that they destroy the labile rickettsial antigen.

Ding has published a series of comparative studies on groups of typhus patients inoculated eight weeks previously with six types of vaccines, thereby producing evidence that the killed vaccines of Cox and other types are active in preventing deaths from typhus. The vaccines tested were Weigl's, Cox's yolk-sac type, Giroud type (rabbit lung) and Combiesco type (dog lung).

Subsection D.—FEVERS CAUSED BY BACTERIA

CHAPTER XII

PLAGUE

Definition.—Plague is a specific, inoculable and otherwise communicable epidemic disease common to man and many of the lower animals. It is characterized by fever, adenitis, a rapid course, a very high mortality, and the presence of a specific bacterium, *Pasteurella pestis* (*Bacillus pestis*), in the lymphatic glands, viscera, and blood. In a large proportion of cases buboes form in the groins, armpits, or neck. The reader is referred to "The Conquest of Plague" (Hirst, 1953).

Geographical distribution.—Probably plague is always present in some part of India and in Uganda, especially among the rude hill-people. It is known to have been endemic in the south-west of China, in the province of Yunnan, for many years. The extension of plague probably had its origin in that part of China, and it is safe to prophesy that it will continue epidemic in that country for many years to come. Japan and the Philippines were both infected from China.

Imported from Hong Kong, the disease appeared in 1896 in Bombay. and subsequently, as a great epidemic, spread to Calcutta and to many other parts of India, where it still prevails. In 1913 plague spread from Negapatam to Ceylon and in 1914 broke out in epidemic form for the first time in Colombo, where it remained confined to one portion of the city. India has suffered more than any other country; there have been years when the plague deaths exceeded a million, and they were considerably above that figure in 1907. It has been estimated that from the time of its introduction into India until that date there was a total of nearly ten million deaths. Soon after its appearance in India, plague became extensively epidemic in Mauritius and it still prevails there at certain seasons. Mombasa and British East Africa (including Nairobi), the West African colonies, Madagascar, Delagoa Bay, Cape Town, Port Elizabeth, and Durban, also Sydney and Brisbane in Australia, and Alexandria in Egypt have all been invaded. Plague was introduced into Java in 1910, and has existed ever since in one of the most densely populated areas in the world. There has been an average of 3,000 to 6,000 cases per annum.

Until its appearance in Brazil, Argentina, and other South American countries, in San Francisco and Mexico, plague had never invaded the Western hemisphere; now it is of considerable importance in California. Peru, into which the disease was introduced from India in 1903, was the first country on the West Coast of South America to be invaded. The infection reached Ecuador through Guayaquil and raged at an altitude of 10,000 feet. Plague was reported from Malta, N. Africa, Egypt, Israel, Italy, Sicily, Rhodes and Corsica in 1945. In recent years plague has reappeared in Calcutta from which the town has been free since 1926.

Active foci of plague are now restricted to (1) Asiatic countries such as India, Burma, Siam, Indo-China, Java and China; (2) African countries, Azores, Morocco, Senegal, Kenya, Tanganyika, Belgian Congo, Madagascar, S. Africa; (3) S. American countries, Peru, Bolivia, Argentina. Selvatic plague tends to spread in N. and S. America and S. Africa.

Epidemiology and endemiology.—Age, sex and occupation have very little influence in plague. The youngest children are susceptible.

Atmospheric temperatures, if very high or very low, seem to have a repressing effect. On the other hand, plague on more than one occasion has flourished during a Russian winter. On the whole, the evidence points to moderate temperature—50° to 80° F.—combined with a certain degree of dampness as being the principal atmospheric condition favouring epidemic outbreaks and recurrences. In Hong Kong, for instance, it was found by Uttley that a mean temperature of 63° F. with a relative humidity of 83° and aqueous vapour tension of 0.500 favours the spread of plague, but when the temperature reaches 82-83° F. or more, for three to four months, with a vapour tension of 0-900, this disease tends to die out.

In large towns and in some districts in which plague recurs for several years in succession there is a seasonal periodicity (which may not be the same in all places) of maximum and minimum prevalence.

The duration of epidemics of plague is very variable. In large cities— Bombay, Hong Kong, Canton, for example—the disease, when fairly established, may not relax its grip for ten or more years. In smaller towns it may disappear in a few months.

The extension of plague epidemics is peculiar: the disease follows trade routes, and especially the grain trade. Sometimes it may spread rapidly from point to point; more generally it creeps slowly from one village to another, from one street or one house to another. Sometimes it skips a house, a village, or a district. In former times it was spread in the Mediterranean by cotton and woollen goods (Hirst, 1953).

These and many other facts in the epidemiology of plague are to be explained by the connection of the disease with the rat and its fleas, and depend in the main upon the migrations of the former and the breeding

seasons of the latter.

ÆTIOLOGY.

The micro-organism.—The specific cause of plague is the bacillus which was discovered by Yersin and Kitasato in 1894. It occurs in great profusion in the characteristic buboes, generally in pure culture, although towards the later stages it is often associated with the streptococci and staphylococci of suppuration. It is present, also, in great abundance in the spleen, intestines, lungs, kidneys, liver and other viscera and, though in smaller numbers, in the blood, while in the pneumonic type it is found in the sputum in profusion. It may be found also in the urine Towards the termination of rapidly fatal cases it occurs in great numbers in the blood.

Pasteurella pestis (Fig. 44), as seen in a blood-film, or in preparations from any of the other tissues, is a short, thick cocco-bacillus (1.5 to 2 by 0.5 to 0.7 μ) with rounded ends, very like the bacillus of chicken cholera. A capsule, or the appearance of one, can generally be made out, especially in bacilli in the blood.

The organism is readily stained by aniline dyes, especially by Romanowsky stains, the extremities taking on a deeper colour than the interpolar part, giving a bipolar appearance. Epstein regards bipolarity as a phenomenon not specially confined to *P. pestis*; the fixing and staining of the specimen naturally influence the result.

Bhatnagar states that virulent stains of *P. pestis* can be recognized by the abundance of the envelope substance.

It is non-motile, Gram-negative, indol-positive, and gives nitrite reaction with sulphanilic acid and X naphthylamine.

with sulphanilic acid and X naphthylamine.

Cultural characters.—When sown on blood-serum and kept at body-temperature

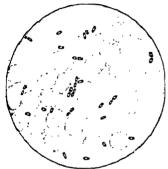


Fig. 44.—P. pestis in peripheral blood in septicæmic plague. ×500. (Microphotograph: Dr. J. Bell.)

in from twenty-four to forty-eight hours an abundant moist, yellowish-grey growth is formed without liquefaction of the culture medium. On agar, but better on glycerin-agar, the growths have a grevishwhite appearance. In agar plate cultures they show a bluish translucence, individual colonies being circular, with slightly irregular contours and a moist surface; on mannite-neutral-red-bile-salt agar the colonies are bright red, but are colourless on a similar medium in which lactose is substituted for mannite. Litmusmilk and glucose-broth are rendered slightly acid; lactose-broth is unchanged. Young colonies are glass-like, but older ones are thick at the centre and more opaque: they are singularly coherent and may be removed en bloc with a platinum needle.

cultures show after one or two days a fine dust-like line of growth. According to Yersin, when sown on gelatin, the bacillus gives rise to white transparent colonies which, when examined in reflected light, present irridescent borders. In bouillon the cultures present a characteristic appearance: the liquid remains clear, whilst a granular deposit takes place on the sides and bottom of the tube. Cultivated on broth in which clarified butter or coco-nut oil is floated, *P. pestis* presents characteristic stalactite growths which gradually fall off, forming a granular deposit. Examined with the microscope, these various cultures show chains of a short bacillus, presenting here and there large bulbous swellings. In gelatin the bacilli sometimes form fine threads, sometimes thick bundles made up of many laterally-agglomerated bacteria, and involution forms are common. The bacillus does not produce spores.

The most favourable temperature for culture is from 36° to 39° C.

The bacillus of plague can be modified by artificial methods; it is well known that some process of this kind takes place in nature, for as a plague epidemic decreases, so the case-mortality falls.

Experimental plague.—In the guinea-pig, within a few hours of the introduction of the bacillus, a considerable amount of cedema appears around the puncture, and the adjacent gland is perceptibly swollen. At the end of twenty-four hours the animal is very ill; its coat is rough and staring; it refuses food, and presently becomes convulsed and usually dies on the third or fourth day. If the body is opened immediately after death a sanguineous cedema is found at the point of inoculation, with hæmorrhagic inflammatory effusions around the nearest lymphatic gland which is much swollen and full of bacilli. The intestines are hyperæmic; the adrenals, kidneys, and liver are red and swollen.

The much-enlarged spleen frequently presents an eruption of small whitish granulations resembling miliary tubercles. All the organs, and even any serous fluid that may be present in peritoneum or pleura, contain plague bacilli. In the blood, besides those free in the liquor sanguinis, bacilli are found in the mononuclear, though not, it is said, in the polymorphonuclear leucocytes.

Rôle of the rat in plague.—Although small and circumscribed epidemics of plague may occur without the intervention of the rat, as when it first appeared in Colombo, there can be no doubt that in most epidemics of the bubonic form this rodent plays an important part, both in the introduction and in the spread of infection. The species principally concerned are Rattus norvegicus (or decumanus), the grey rat, and Rattus rattus, the black rat (Figs. 45 and 46). The mouse, Mus musculus, is also

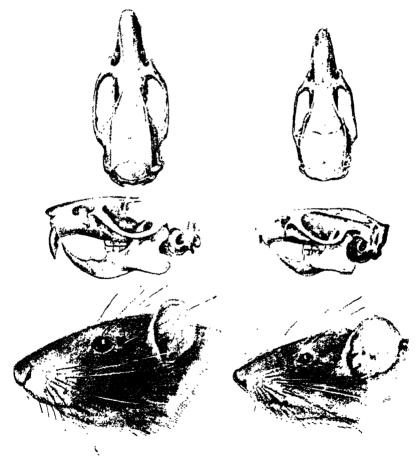


Fig. 45.—Rattus norvegicus.

Configuration and anatomical characters of head and skull (nat. size).

Fig. 46.—Rattus rattus.

Configuration and anatomical characters of head and skull (nat. size).

susceptible. The bandicoot and musk rat are of little importance in these respects, although susceptible to laboratory infection. In Bombay the epizoötic appears first in the Rattus norvegicus community, Rattus rattus—the more domestic species—being subsequently attacked. Later the disease appears in epidemic form in man (Chart 13).

The seasonal prevalence of bubonic plague in rats is marked and is not due to a periodicity in their reproduction, but is connected with periods in which fleas are most numerous. In places in which plague epidemics keep recurring year after year the local rats acquire a considerable degree of immunity; moreover, this is transmitted hereditarily.

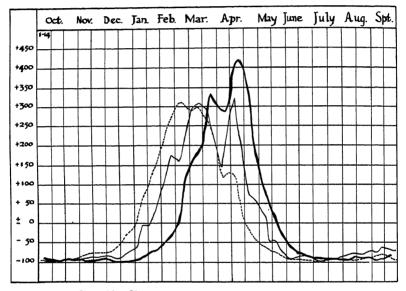


Chart 13. . Showing progress of plague in rats and man.

("Report of Indian Plague Commission.")

...... Infected R. norvegicus.
Infected R. rattus.
Human deaths from plague.

Thus, in plague-free towns in India—e.g. Madras and Dacca—the mortality among the local black rats experimentally infected was 100 per cent., while in plague-stricken towns, such as Cawnpore and Poona, it was much less.

Another observation which may have important bearings on the spread of plague, and the yearly recurrence of epidemics in the same place, is that in certain rats the disease may assume a chronic form.

Other animals may die of plague during an epidemic; dogs are said to be immune.

History.—Although the main credit is given to the Indian Plague Commission for the part it played in elucidating the transmission from rat to man, yet it is an astonishing fact that the pioneer studies of P. L. Simond (Ann. Inst. Pasleur,

1893) have been forgotten and his conclusions neglected, for now it appears that many of the generally accepted facts of plague were enunciated by him for the first time. That it is primarily a disease of rats was recognized by Yersin and Roux in 1897 and the rôle of fleas as vectors of the infection suggested by Ogata in the same year, but it was Simond who, after a brief visit to India, found that the outbreak of plague in rats was followed by an epidemic in man; furthermore he found plague bacilli in fleas and noted that the primary lesion in man was often a blister containing plague organisms. He noted that fleas leave the body of a stricken rat and found that the bacilli could be conveyed by the bite of a flea. He tried out the mouse-protection test as a measure of the efficacy of antiplague serum and finally suggested sulphuric acid fumes as a means of rat destruction in ships.

Selvatic (sylvatic) or wild rodent plague.—Formerly, epidemiologists concerned themselves mainly with rat epizoötics, but recently, increasing attention is being paid to plague of wild rodents of the fields and woods field-rodent, or selvatic, plague. It is now realized that plague exists in a smouldering state over vast tracts of territory among the Asiatic marmots; among the "susliks," mice and jerboas of the desert region of south-eastern Russia; among the gerbilles and muridoe of the African high veld and coastal region; among the chipmunks and ground-squirrels of California; and in South America among the cavies ("cuis," wild guinea-pigs), and other peculiar rodents of the Pampas. In Chile, on the other hand, plague is restricted almost entirely to rats in the seaports. Desert country is unfavourable to the rat flea, Xenopsylla cheopis. Although field-rodent plague has given rise so far to comparatively little human mortality in most countries, in North Manchuria, where the disease is endemic in the marmot or "tarabagan," virulent epidemics of pneumonic plague have occurred.

Rôle of the marmot and other rodents.—Mongolian and Siberian pneumonic plague epidemics are associated with the occurrence of the disease in species of marmot known as "tarabagan" (Arctomys bobac, Fig. 47),¹ and several smaller species (Citellus citellus, C. pygmæus and C. mugozaricus), locally known as "susliks," which can harbour the plague bacillus in their bodies without apparently suffering any ill effects during hibernation, thus constituting a more or less permanent reservoir of the plague virus. Possibly plague infection is transmitted to man by the fleas which infest these animals, but it is more generally considered that the rodent fleas play a minor part and that the infection is transmissible via the alimentary tract. It has been shown that in hibernating spermophiles P. pestis loses its virulence and is less easily cultivated. Epizoötics of plague in these regions generally begin after hibernation.

The pouched marmot of the Caucasus (Spermophilus guttatus) is extremely susceptible to plague infection and is probably concerned in the spread of the disease in that region. In Transbaikalia plague occurs in Spermophilus eversmani and in S. dauricus, which are 22 cm. long and rather resemble the tarabagan. The presence of spermophiles, which are related to marmots and ground-squirrels, can be determined by the characteristic excrement at the mouth of their burrows.

¹ A subspecies of A. bohac, Arctomys centralis, was found infected in the Narinsk epidemic of 1929-30.

As an indication of the important part that many animals play in the spread of human plague, extracts from the report of the first Plague Congress of Soviet Russia, 1927, may be taken as an example. In South-East Russia, from October, 1925, to May, 1927, there were 42 plague epidemics with 310 cases. The infection of 11 of these originated from



Fig. 47.—Arctomys bobac, Siberian marmot (nat. size).



Fig. 48.—Citellus beecheyi, ground-squirrel of California (nat. size).

domestic and field mice. four from spermophiles. three from jerboas (Dipodipus sagita), and four from gerbilles (Rhombomys opimus), while seven outbreaks were traced to infection at slaughter of plagueinfected camels. Fleas capable of biting man were found on nearly every rodent and they play an active part in the spread of plague in Russia. Proventricular blocking (see p. 267) with the plague bacillus occurs in the gerbille fleas (Ceratophyllus tesquorum and C. læviceps).

Plague is known to the exist $_{
m in}$ seven states western America, but it has not so far been noted east of Wyoming nor south of Utah, save in California; the most northerly point is some 150 miles north of the Californian border. California the groundsquirrel (Citellus beecheyi, Fig. 48), although it does not live near human habitations, in-

fects rats that do, and thereby acts as an important reservoir of P. pestis.

Seven species of ground-squirrel are now known to harbour plague including Citellus beecheyi, C. fisheri, C. grammurus, and C. tounsendi. Other wild rodents from which plague-infected fleas have been collected include tree-squirrels (Sciurus douglasti, Xerus erythropus), chipmunks (Tamias sp.), marmots (Marmota flaviventer nosophora, M. fl. engelhardti),

prairie dogs (Cynomys parvidens), and a field-rat (Arvicanthus rufinus). Eskey and Haas have pointed out that wild rodent plague in the Western United States is not always accompanied by infection of domestic rats.

In 1946 it was found that the prairie dog (Cynomys gunnisoni) harboured plague and in 1947 rodent plague was reported from six Western States, but only one fatal case in man in California. In New Mexico, in 3,271 rodents, Link found evidence of plague only in prairie dogs and marmots (Marmota flavirostris) or their fleas, but no human cases had been reported. In California the infection is spread from the ground squirrel to the rat and from rat to rat by the fleas (Diamamus montanus and Hoplopsyllus anomalus) (Meyer and Holdenfried).

In Brazil plague was first introduced in 1899 and was a port disease; in the next period it passed to cities in the interior; and now, in the third period, it is tending to disappear from the cities and to localize itself, endemically, in rural areas, associated with storage of food which attracts rodents. In Sao Paulo Xenopsylla brasiliensis is the most important vector.

In South Africa, especially in the Cape Province, the rodents of the inland veld have become infected with plague and, by continuously passing the disease from one to another, constitute a persistent and dangerous source of human infection. On the high veld the gerbilles (Taterona lobengulæ and Desmodillus auricularis), the ground-squirrel (Geosciurus capensis), and the multimammate mouse (Mastomys coucha) are the most important—the latter forming a link by conveying infected fleas from gerbille burrows into human habitations. In the lower bush country the striped mouse (Rhabdomys pumilio) plays the chief rôle, while the springhaas (Pedetes caffer), a giant jerboa, on account of its extreme mobility, is capable of widely disseminating plague. Two carnivores, the suricate and the yellow mongoose, are susceptible to plague by feeding on dead and dying rodents, and it has been pointed out by Mitchell that the discovery of gerbille remains in the fæces of these animals is a valuable indication of the existence of a rodent epizoötic in the veld districts, as these animals do not normally eat gerbilles unless they are sick.

The gerbilles, especially the Namaqua species (D. auriculatus), range both within and without the plague area and extend throughout Africa to the Sahara. Tatera brantsii ranges from the E. Karoo, the high veld, Kalahari, and parts of Natal, T. schinzi from the Kalahari and its borders; but T. afra is not found in the enzootic areas. The flea vector is X. eridos, whose chief host is T. brantsii.

South African rodents harbour a large number of species of flea. Of these, three, Dinopsyllus ellobius ellobius (lypusus), Chiatopsylla rossi and Xenopsylla eridos have been found, under experimental conditions. capable of conveying plague infection. The last-named occurs almost entirely within the enzootic region.

To be effective, the prophylaxis of plague in the wilder regions of the world necessarily entails a knowledge of the habits of these rodents. The ground-squirrels are really spermophiles which constitute a connecting link between

the true squirrels and the marmots. Ground-squirrels are generally found in prairie-like regions, where they construct an intricate system of burrows, at the main entrance of which they may be commonly seen standing on guard upright and motionless.

The true marmots, such as the "tarabagan," are characterized by the rudimentary thumb, small eyes and ears; the tail is bushy and comparatively short. The burrows which they excavate are very deep and are crowned by mounds of earth thrown up by successive generations of marmots and are known as "bootans" in Mongolia. The gerbilles are small jerboas; they are rather smaller than the domestic black rat; the hind legs are long, the front very short. They are pale fawn with white bellies. Their habitat is sandy country where they live in families. Their warrens extend over an area of 30 square yards and to a depth of 3-4 feet. Gerbilles may commonly be seen sitting warily in an upright position at the mouth of their burrows with front paws extended horizontally. The warrens often harbour ground-squirrels, suricates and mongooses, all four species, apparently, living on friendly terms. Plague is spread among gerbilles (Taterona lobengulæ) through the intestinal tract by the cannibalistic habits which these creatures develop when sick.

The multimammate mouse is the wild mouse of the veld and has much the same habits; in country districts it invades human habitations. The striped mouse is diurnal and is more numerous in bushy country, where it usually builds big nests of sticks on the surface of the ground and lives in large families.

In North Africa spontaneous plague is found in the following rodents: Psammonys rondairei, Dipodillus dodsoni, D. campestris, Gerbillus hirtipes and Meriones shawi. In Uganda the rodent reservoir is R. rattus, originally it was R. mastomys (coucha ugandæ) and X. braziliensis is the chief vector.

In Dakar (Senegal) a shrew (Crocidura stampflii), on the Gold Coast, the giant rat (Cricetotomys gambianus), and in Kenya the field rat (Arvicanthus

abyssinicus) play their part in the dissemination of plague.

In South America, in the Argentine pampas, Uriarte and Villazon have shown on several occasions that rodents of the cavy type suffer in plague epizoötics. The species specially concerned are *Microcavia australis* and *M. galea*; a cricelid also, *Graomys griseoflavus*, has been shown to be experimentally very susceptible. It is arboreal, and recently de la Barrera found a small outbreak of human plague which was traced to this animal.

On observations such as these the modern quarantine against plague has been framed.

Rôle of the flea in plague.—It is now known that plague is not communicable from animal to animal by simple contact, but is readily communicated by fleas, and principally by Xenopsylla cheopis (Fig. 403, p. 1069), the rat-flea of the tropics, Ceratophyllus fasciatus, the rat-flea of temperate climates, and Ctenocephalus canis and C. felis, which hite men, dogs and rats indifferently. These act as passive intermediaries and carriers of the bacillus. P. pestis multiplies in the stomach of the flea, retaining its virulence for over twenty days and is then passed out in the fæces, so that the flea serves not only as a carrier, but also as a multiplier of the germs. Wu Lien Teh has shown that in outbreaks of plague in Manchuria the human flea (Pulex irritans) may convey the sacillus direct from patient to patient without the intervention of the rat.

Especially convincing are the experiments of the Indian Plague Commission, which clearly showed that, if fleas are excluded, healthy rats will not contract the disease, even if kept in intimate association with plague-infected rats. Young rats may even be suckled by their plague-stricken mothers and remain healthy. It suffices to transfer fleas from a plague-infected to a healthy animal, or to place the latter in a room in which plague rats had died recently and had been subsequently removed. The fleas that have left the body of the dead rats, remaining in the room, convey the bacillus. An animal placed on the floor cannot be infected, if the precaution is taken to surround the cage with "tangle foot," so as to keep off the fleas; but if it be placed on the unguarded

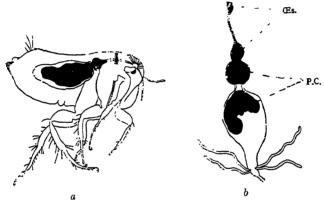


Fig. 49.—a, Flea viewed as a transparent object; the proventriculus and stomach contain a mass of plague-culture.

b, Flea's stomach, obstructed by growth of plague-culture.

CBs., Distended esophagus containing fresh blood; P.C. obstructing mass of plague-culture. This figure illustrates the method of transmission of P. pestis by Ceratophyllus fasciatus. (By permission of Sir C. J. Martin, "Journ. of Hyg.," 3rd Plague Suppl., Jan., 1914.)

floor, either in its cage or allowed to run about, or even if suspended 2 in. above the floor—a distance not beyond the saltatory powers of the flea—it will become infected.

Martin and Bacot found that a proportion of the fleas fed on plague-infected rats develop a peculiar condition of stomach and esophagus, which become blocked with blood-clot containing a pure culture of *P. pestis*. When such a flea feeds on a normal rat, part of the culture regurgitates and communicates infection; at the same time bacilli are passed in the fæces and may infect through any existing abrasion. They further observed that the "blocked" fleas died very rapidly, apparently of thirst, if placed in a warm, dry atmosphere (Fig. 49). There is apparently little difference between wild rodent and domestic rat fleas in the readiness of infection. The life-span of the infected flea is comparatively short; according to Eskey and Haas the average survival is only about 3-2 days. Under experimental conditions some squirrel fleas become blocked as readily as *X. cheopis*.

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In temperate climates fleas are most numerous during the warmer weather; hence, summer and autumn are the bubonic plague seasons. In warm climates bubonic plague is most likely to become epidemic when temperature ranges between 10° and 30° C.—temperatures favourable to the multiplication and activity of the flea. Temperatures over 30° C. are unfavourable, especially if the atmosphere is dry. Pneumonic plague, not being spread by this insect, is not influenced by temperature in this way.

The flea, then, communicates plague either by its fouled mandibles, by regurgitation, in the act of sucking, or by provoking scratching and

consequent inoculation of the bacilli deposited in its fæces.

The capacity of a flea's stomach is about ½ c.mm. and in most cases of human bubonic plague there are not sufficient plague bacilli in the peripheral blood-stream to infect it with any regularity, except in the terminal stages of fatal cases. The "cheopis index" is regarded as important by sanitarians, i.e., the number of fleas per rat. An index of over 5 is likely to produce an outbreak of bubonic plague. The human flea, Pulex irritans, which occurs in enormous numbers, especially in Morocco, may become infected; but there is no convincing evidence to show that it ever plays a dominant part in the spread of plague.

It has long been known that large tracts of country and important cities in India, such as Madras, have remained immune from plague, though in constant communication with plague-infected centres. In 1914 Rothschild and Jordan pointed out that the rat-fleas of Indian cities belonged to three closely allied species—X. cheopis, brasiliensis, and astia—and soon afterwards Hirst and Cragg discovered that in those districts, in which plague was uncommon, X. astia replaced X. cheopis as the common ectoparasite of the rat. From this and other experimental evidence it is now assumed that this species is unable to convey the plague infection in the same manner as X. cheopis (see p. 1070).

Bionomics of the rat-flea.—In ordinary circumstances the rat-flea completes its developmental cycle in from fourteen days to three weeks, but in warm damp weather this may be shortened to ten days. It requires ideal tropical conditions for propagation. The average life of a flea, separated from its host, is about ten days, but it is capable of remaining alive without food for two months, should the temperature of the air be low. In tropical temperatures the insect can harbour the plague bacillus without feeding on blood for forty-five days. In Madagascar it has been shown that rat-fleas (X. cheopis) may survive in dust and spread infection long after the bodies of the defunct rats have disappeared. These fleas can survive in cotton goods.

Apart from the very serious danger arising from vermin infected with chronic plague, which may hang about a house, the house itself does not retain the infection for any length of time. The Plague Commission has shown that floors of cow-dung contaminated with *P. pestis* do not remain infective for more than forty-eight hours and that floors of "chunam" cease to be so in twenty-four hours.

live in the roofs of native houses usually fall down on to the floor when stricken with plague. Leina and Hathaway (1947) have compiled a bibliography of fleas and their animal hosts; Chabaud (1947) a list of rodents and fleas in selvatic plague.

Pathology.—After death from plague the surface of the body very frequently presents numerous ecchymotic spots or patches. The number and extent of these vary, apparently, in different epidemics. In some epidemics the cutaneous hæmorrhages have been both extensive and numerous. The characteristic buboes are generally apparent; occasionally there are also furuncles, pustules, and abscesses. Rigor mortis is usually moderate; sometimes post-mortem muscular contractions, like those in cholera, take place. Post-mortem rise of temperature is often observed. Decomposition is said to set in early.

The characteristic appearance of plague in a necropsy is that of engorgement and hæmorrhage, nearly every organ of the body participating more or less. There is also parenchymatous degeneration in most of the organs. The brain, spinal cord, and their meninges are markedly congested, and there may be an increase of subarachnoid and ventricular fluid. There are numerous and pronounced puncta cruents on the brain sections; occasionally there may be considerable extravasations of blood into the substance of the brain (mesen-

cephalon and medulla oblongata).

Ecchymoses are common in all serous surfaces; the contents of the different serous cavities may be sanguineous. Extensive hæmorrhages are occasionally found in the peritoneum, mediastinum, trachea, bowel, stomach, pelvis of kidney, ureter, bladder, or in the pleural cavities. The lung frequently shows evidences of bronchitis and hypostatic pneumonia; sometimes hæmorrhagic infarcts and abscesses are found. The right side of the heart and the great veins are usually distended with feebly coagulated or fluid blood. In pneumonic plague the superficial lymphatic glands are not enlarged; the pleural cavities contain blood-stained serum; the infected lungs are deeply congested and edematous, and at a later stage pneumonic consolidation is found. The bronchi contain blood-stained serum, and the bronchial glands are swollen and hæmorrhagic.

The liver is congested and swollen, its cells are degenerated and may be the seat of miliary plague abscesses. The spleen is enlarged to two or three times its normal size. The kidneys are in a similar condition. The mucosa of the alimentary canal as a whole is congested, showing here and there punctate ecohymotic effusions and, occasionally, hæmorrhagic erosions, and even—especially about the ileo-cæcal valve—ulcerations.

The lymphatic system is always involved; around the glands there is much exudation and hæmorrhagic effusion, with hyperplasia of the gland-cells and

enormous multiplication of plague bacilli.

Symptoms. Incubation period.—Symptoms of plague begin to show themselves after an incubation period of from 2-8, rarely 15 days.

The average case of plague: prodromal stage.—In a certain but small proportion of cases there is a prodromal stage characterized by physical and mental depression, anorexia, aching of the limbs, feelings of chilliness, giddiness, palpitations and sometimes dull pains in the groin at the seat of the future bubo.

Pestis minor, or ambulatory stage.—Abortive or ambulatory cases of bubonic plague have been reported in connection with almost every true outbreak of the disease and in some constitute a high proportion. Joltrain reported several of these cases in the Paris outbreak of 1920 and also in Algeria; Leger described similar cases in Dakar and Fonqueraie

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in Madagascar. Clinically these cases present mild, general febrile symptoms with a bubo, and when that suppurates the temperature falls, and the patient recovers. The diagnosis may be difficult because the plague bacillus may be very scanty in the pus. The differential diagnosis has to be made from climatic bubo (Lymphogranuloma venereum).

From the clinical aspect, plague in man can be divided into the following varieties:— (1) Bubonic (2) Septicæmic (3) Pneumonic and (4) Meningeal.

Bubonic plague.—This is the most common form and constitutes about three-quarters of the total number. The incubation period is usually very short; generally within twenty-four hours the characteristic bubo, or buboes, develop. According to Pollitzer (1945) it is possible to distinguish three varieties of bubonic plague: (1) well-marked bubonic infection not leading to secondary septicæmia, (2) bubonic affection followed by secondary septicæmia, (3) serious general septicæmia combined with slight affection of lymph glands. Generally (in 70 per cent.) the bubo appears in the groin, especially on the right side and affecting one or more of the femoral glands; less frequently (20 per cent.) the axillary; more rarely still (10 per cent., especially seen in children) the submaxillary lymphatic glands may be the seat of the bubo, while the tonsil may be the primary focus of infection. In rare instances cervical buboes may actually result. Buboes are usually single, but in about one-eighth of the cases they form simultaneously on both sides of the body. Very rarely bubbes form in the popliteal, epitrochlear, or clavicular glands. Occasionally they develop simultaneously in different parts of the body. A curious point noted in North West America is that in squirrel-conveyed plague axillary buboes are common. Plague buboes vary very much in size. Sometimes they are not as large as a walnut; in others again they may be as large as a goose's egg. Pain may be very severe, but sometimes it is hardly felt. Besides the enlargement of the gland there is, in most instances, considerable pericellular infiltration and cedema.

Stage of fever.—The stage of invasion may last for a day or two without serious pyrexia, but usually it is much shorter, or it may be altogether absent. The disease usually develops abruptly, without a definite rigor or other warning, the thermometer rising rapidly to 103° or 104°, or even to 107° F., with corresponding acceleration of temperature and pulse. The temperature usually falls after three or four days and then rises again. The skin is now dry and burning, with bloated face; the eyes congested, sunken and staring; hearing is dulled. The tongue is swollen, covered with thick creamy fur, which dries rapidly and soon becomes brown or almost black. Sordes form on the teeth and about the lips and nostrils. Thirst is intense; prostration extreme, whilst from utter debility the voice is reduced to a whisper. Sometimes there is wildly

fatuous delirium, or it may be of the low muttering type.

Coma, convulsions—sometimes tetanic—retention of urine, subsultus tendinum and other nervous phenomena ensue. Vomiting is in certain cases very frequent. Some patients are constipated, but in others there is diarrhesa. The spleen and liver are usually enlarged. Urine is scanty, but rarely contains more than a trace of albumin. The pulse at first

full and bounding, in the majority rapidly loses tone, becoming small, frequent, fluttering, dicrotic and intermittent. In the later stages the heart is usually dilated, the first sound being feeble or absent altogether. Hæmorrhages are seen on the mucuous membranes in severe cases. There is usually a polymorphonuclear leucocytosis.

Stage of recovery.—In favourable cases, sooner or later, after or without the appearance of the bubo, the constitutional symptoms abate with the setting in of profuse perspiration. The tongue begins to moisten, the pulse-rate and temperature to fall, and the delirium to abate. The bubo, however, continues to enlarge and to soften. After a few days, if not incised, it bursts and discharges pus and sloughs—sometimes very ill-smelling. In rare instances suppuration is delayed for weeks; whilst in some the bubo subsides after a few weeks, or perhaps months, without having broken down. The sores left by the buboes and abscesses of plague are extremely indolent and may take months to heal. Owing to contracture and fibrosis of lymphatic tissue, edema of the leg on the affected side usually supervenes. Convalescence sets in some time between the sixth and tenth day, although it may be delayed for a fortnight or three weeks.

Skin affections.—In a very small proportion of cases what are usually described as carbuncles, in reality small patches of moist gangrenous skin that may gradually involve a large area, develop on different parts of the integument. These occur either in the early stage or late. Sometimes they slough and lead to extensive gangrene.

Kirk and Crawford have described a generalized papular rash on the hands, feet and pectoral region. Should life be continued sufficiently long, the vesicles become converted into pustules resembling smallpox. These observations confirm in a remarkable manner, as MacArthur has pointed out, the old writers who described manifestations, in the Plague of London of 1665, as "blains."

Complications.—Occasionally a pyæmic condition, with boils, abscesses, cellulitis, parotitis, or secondary adenitis, succeeds the primary fever. During convalescence tragic sudden cardiac failure is not uncommon. Secondary pneumonic plague with blood-stained sputum may supervene, but the patient may recover.

Hæmorrhages of different kinds are not an unusual feature of plague—ecchymotic effusions of a purplish or dull-red tint, varying in size from a hemp-seed to half an inch in diameter. These are found frequently in certain malignant epidemics.

Abortion almost invariably occurs in pregnant women; the fœtus sometimes shows signs of the disease.

Death may take place at any time. Usually it occurs between the third and fifth day, with symptoms of profound adynamia, heart-failure, or perhaps from convulsions, from coma, from internal hæmorrhage or, later, from exhaustion consequent upon prolonged fever or suppuration, or from secondary hæmorrhages.

Septicæmic plague, or pestis siderans.—In this type there is no special enlargement of the lymphatic glands during life, although after death throughout the body they are somewhat enlarged and congested. The

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high degree of virulence and the rapid course of the disease depend on the entry of large numbers of the bacilli into the blood, where they can be readily found during life. The patient is prostrated from the outset; he is pale and apathetic; there is generally little febrile reaction (100° F.). Great weakness, delirium, picking of the bed-clothes, stupor and coma end in death on the first, second, or third day, or, it may be, later. Frequently in these cases there are hæmorrhages.

It is probable that in many cases of bubonic plague there is some degree of septicæmia, and that in a minority of cases this may progress to the

full septicæmic type, or may give rise to plague pneumonia.

Pneumonic plague.—This occurs frequently in epidemic form among the marmot-trappers of Northern China, who live under very insanitary conditions, but may occur spontaneously wherever the bubonic form is found. It is especially dangerous to the patients, attendants, and visitors, because of the multitude of bacilli which are scattered about in the patient's expectoration, because the clinical symptoms are unlike those of typical plague and are apt to be mistaken for some ordinary form of lung disease. The illness commences with rigor, malaise, intense headache, vomiting, general pains, fever, and intense prostration. In the early stages there may be little to suggest pneumonic plague, except the marked discrepancy between the almost negligible physical signs and the gravity of the patient's condition. Cough and dyspnœa set in, accompanied by a profuse, watery, blood-tinged sputum. The sputum is not viscid and rusty, as in ordinary pneumonia. From the outset clouding of consciousness is very marked. Moist râles are audible at the bases of the lungs, the breathing becomes hurried, other symptoms rapidly become worse, delirium sets in, and the patient usually dies on the fourth or fifth day. This is the most fatal as well as the most directly infectious form of plague. A single spontaneous recovery has been reported from South Africa (Clark and Goldberg, 1943). Epidemics of 50,000 and more cases have occurred in Manchuria, where the plague bacillus exists as an intestinal infection in the marmot which acts as a reservoir of the bacillus. Pneumonic plague has been recorded from Nigeria, the Gold Coast, Ecuador, New Orleans and elsewhere. In these countries hemorrhage into the intestinal canal occurs in about 8 per cent. of plague-infected rats and the organism is passed out in the fæces; in this manner the plague bacillus can be disseminated in dust and inspired by man directly into the (Connal and Paisley.) Murdock believes that secondary plague pneumonia occur in a proportion of patients with bubonic plague and that the disease is then spread by droplet infection and inhalation. Pneumonic plague is exceedingly dangerous to nurses and others in contact with the patients.

by Williams from East Africa and by Devignat from the Congo, by Pollitzer, Landsborough (1947) and others from Chuanchow, South China. From South America cases have been reported by Lastra and Rodeiro (1944). In all except the first named meningeal involvement was a complication of the bubonic form from the ninth to seventeenth days. In clinical features it rather resembles cerebro-spinal meningitis with painful headaches, stiff neck and Kernig's sign. Special symptoms are meningeal irritation, convulsions, vestibulo-cerebellar symptoms and coma. Primary plague meningitis is a pyrexial illness with meningeal irritation, from which P. pestis is obtained by lumbar puncture. The cerebrospinal fluid is under pressure and yellow in colour closely resembling that of acute suppurative meningitis. The initial infection is probably due to droplet infection. The brain shows congestion and flattening of sulci and is covered with a thick fibrinopurulent exudate.

Relapses.—Relapses have been recorded in bubonic plague and are specially dangerous.

Mortality.--The case-mortality of bubonic plague varies in different epidemics. It is usually greatest at the beginning and height of the epidemic. The death-rate may be anything from 60 to 95 per cent. of those attacked. Much appears to depend on the social condition of the patient and the attention and nursing available. Thus, in a Hong Kong epidemic, while the case-mortality among the indifferently fed, overcrowded, unwashed, and almost unnursed Chinese amounted to 93.4 per cent., it was only 77 per cent. among the Indians, 60 per cent. among the Japanese, and 18-2 per cent. among the Europeans—a gradation in general correspondence with the social and hygienic conditions of the different nationalities. In the South American epidemics and in the recent circumscribed epidemics in Europe the mortality was only about one-third of that in India and China. Pneumonic plague is generally fatal in from three to four days. Van den Berg and Vos report that in an epidemic in Java (1930) in 66 cases of plague the mortality was 76 per cent. The sixteen who recovered had all been suffering from bubonic plague. The chances of recovery were somewhat better in men than in women. In this series there were 57 cases of bubonic plague, two of plague ulcers. 29 of septicæmic plague, and one of primary plague pneumonia.

Diagnosis.—Fever and adenitis during a plague epidemic must invariably be viewed with suspicion, and particularly if the fever rapidly assumes an adynamic character. In the early stages diagnosis may be very doubtful, especially in pneumonic plague and in the countries of high filarial endemicity in which filarial adenitis is common. Blood-culture was recommended by Onoto, by inoculating blood into broth containing 1 per cent. of sodium citrate. Rosier stated that in Java splenic puncture is valuable in establishing a diagnosis and is not opposed by the native population. Junior and de Albuquerque described an allergic skin test for which an emulsion of infected guinea-pig lymph gland is used. In Western America the differentiation of mild cases

of plague from tularæmia is important (p. 284). The discovery of the bacillus in the glands, blood, sputum, or discharges is the only thoroughly reliable test. Should a cocco-bacillus be found with the characteristic bipolar staining, it should be cultivated by Haffkine's method in broth on which clarified butter (ghee) or coco-nut oil is floated (see p. 260). In case of doubt, animal inoculation should be used; a little of the virus from the patient or a culture is rubbed into a shaven area (1 in. square) on the abdomen of a white rat or a guinea-pig. P. pestis inoculated in this way kills the guinea-pig in seven days, the rat sooner and white mice in forty-eight hours. The latter may be inoculated at the root of the tail.

Post-mortem indications of plague in the rat.—Before rats suspected of being plague-infected are handled, they should be immersed in disinfectant to destroy

ectoparasites.

The lymphatic glands should be first exposed. If the rat is infected, subcutaneous injection around the glands is generally recognizable. If the gland is itself inflamed, this is almost diagnostic of plague; the liver will be yellow, sprinkled with innumerable pinky-white granules. The spleen is enlarged, congested, and occasionally granular. The serous membranes are of dull lustre with petechial or diffuse hæmorrhages. Serous or blood-stained serous effusions are present in 72 per cent. of such rats; if, on microscopical examination of scrapings from glands or spleen, bipolar-staining bacilli are detected, the case is probably plague. Too great stress must not be laid on bipolar staining alone, as this feature depends somewhat on the method; it is best demonstrated by the Leishman eosinazur stain. P. pestis persists for a long period in the bone marrow of plague rats, even after putrefaction has set in.

P. pestis, P. pseudotuberculosis rodentium, P. suiseptica and P. aviseptica closely resemble each other and are scarcely distinguishable by the usual cultural methods, but the latter two have no "envelope substance," though they have a common antigen with P. pestis. None coagulates milk, but in agar P. pestis produces a more glistening membranous growth. P. pseudotuberculosis rodentium produces a clear, yellowish growth on potato. On Drigalski medium it produces blue colonies: P. pestis reddish ones. P. pseudotuberculosis readily associates itself with the production of smooth and rough colonies with all degree of transitions between them. The smooth colonies show closest association to P. pestis and are the most virulent. P. aviseptica produces indol and does not reduce

methyl red.

The most satisfactory means of differentiation is animal inoculation. Rabbits, guinea-pigs, and white mice are susceptible to *Pasteurella pseudotuberculosis*, but white rats are not. The Indian Plague Commission laid stress on the latter point, as these animals are instantly killed by *P. pestis*. These organisms belong to the hæmorrhagic septicæmia group. Gunnison and colleagues differentiate these organisms by bacteriophage.

Rodent plague and fleas.—In the investigation of rodent plague the inoculation into animals of pooled fleas is important. Cyanide gas is the best method of collecting fleas from rodents. The long bones of rodents may be sent to the laboratory for culture tests of marrow.

Differential diagnosis.—Bubonic plague has sometimes to be distinguished from other affections associated with enlarged glands, such as streptococcal infections, lymphogranuloma venereum, filarial adenitis, and occasionally from an anthrax pustule.

In filarial and streptococcal infections lymphangitis tracks are usually visible, but in bubonic plague there is usually no visible sign of the primary infection. In glandular fever the cervical glands are as a rule primarily affected and there is an excess of heterophil antibodies in the serum (goat's corpuscle test).

Generalized pustular plague has to be differentiated from chickenpox or smallpox; carbuncular plague may be mistaken for anthrax; septicæmic plague may be confused with typhus and subtertian malaria. In the United States, North Europe and Russia, tularæmia may resemble

plague.

Pneumonic plague differs from other forms of pneumonia in three main characteristics: (1) The patient is extremely prostrated, although his critical state can hardly be accounted for by such physical signs as are present in the chest; but by the time definite involvement of the lung can be demonstrated, he generally dies. (2) The sputum is watery, never thick, and soon becomes very blood-stained. (3) Pleural effusion is usually present in plague pneumonia.

Treatment.—During the earlier stages, when headache and perhaps high fever are urgent, much relief may be obtained from ice-bags to the head and neck. If it be deemed advisable to attempt to lower the temperature, sponging the body every hour with warm water is a much safer measure than antipyrin and similar drugs. If diarrhea be present, Lowson recommended ice pills and an effervescing mixture containing morphia and hydrocyanic acid. Sinapisms to the epigastrium are useful. Given with judgment, morphia is by far the best hypnotic. Hyoscine $(\frac{1}{200}$ to $\frac{1}{75}$ gr.) or chloral (20 gr.) and bromide of potassium (30 gr.) are of service for the same purpose.

The buboes in the early stage may be treated with applications of glycerin and belladonna. Should they become red and inflamed, they must be poulticed and, when they soften, incised and dressed with iodoform. Indolent bubonic swellings should be treated with iodine liniment. The injection directly into the buboes of iodine and a solution of camphor and thymol mixed in equal parts, in doses of $\frac{1}{2}$ to 1 ml., according to the

age of the patient, has been advocated.

Serum therapy.—Yersin, Calmette, and Borrel immunized a horse by intravenous injections of living virulent cultures and produced an effective antiserum. In septicæmic plague it must be given intravenously in large doses (100–250 ml.), and frequently repeated, but, to be effective, must be administered early in the course of the disease. Anti-plague serum has been tried in India. Dawson reported that in bubonic plague, in doses of 30–40 ml., the results have been encouraging. Injections in and around the bubo were advocated by Bonebakker. E.V., an avirulent strain of *P. pestis*, is used for producing this serum.

Sulphonamides.—Durand, Girard, Schütze and others showed that certain sulphonamides, especially sulphapyridine, protect mice infected with plague, if combined with anti-plague serum. According to reports from India and America the combined therapy of immune serum with sulphonamides has obtained increasing support, but all are agreed that

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when septicemia has occurred the outlook is serious. Sulphathiazole is advocated by the Haffkine Institute in Bombay-10 grm. on the first and 7.5 grm. per day for a further four or five. A smaller dose can be given later with a concentration of 5-10 mgm. per cent. Jawetz and Mever (1944) claim that the treatment of choice is obtained by the use of hyperimmune serum combined with chemotherapy. The serum is obtained from rabbits which have been given three intravenous injections of living virulent P. pestis on alternate days. Nagle (1944) favours sulphadiazine. Altogether 180 cases of plague, differentiations of septicemic from nonsepticæmic, were treated in strictly alternate succession, 89 with sulphathiazole and 91 with sulphadiazine. The mortalities were 33.7 and 21.9 per cent. respectively. This should be compared with previous trial of iodine intravenously when the mortality of a comparable series was 58.1 per cent. Sulphadiazine was administered in an initial dose of 4 grm.. followed by 2 grm. four hours later and 1 grm. every four hours. The patient received 10 grm. the first day and 6 grm. on subsequent days. All serious cases received 2 grm. of initial dose intravenously. patients were encouraged to drink 1,200-1,500 ml. of fluid daily.

Streptomycin exerts an action on P. pestis comparable with that on Br. tularensis. It has been tried out experimentally on mice and inhibits the growth of P. pestis in vitro in concentrations of three units. When injected subcutaneously in mice it gives an 85 per cent. survival rate in doses sufficient to kill 100 per cent. of control animals. It is also effective in curing artificially produced plague pneumonia in guinea-pigs (Herbert,

1947).

The first two human cases were treated with streptomycin at Buenos Aires (1947) and though the prognosis appeared hopeless, the patients survived. This miraculous result has now been confirmed (1948) by Karamchandani and Rao (1948) in five moribund patients at Antapur, Madras. Streptomycin, 0.5 grm., was given intramuscularly six-hourly for 72–96 hours up to a maximum of 8.0 grm. Since that time recoveries even from pneumonic plague have been reported by Lewin and colleagues (1948) in doses of 1.8 grm. of streptomycin daily for 8 days, with a total of 24 grm. of sulphadiazine. On the ninth day the temperature fell to normal and plague bacilli could no longer be found in the sputum.

Combined treatment.—Wagle believes that sulphadiazine is the best of the sulphonamides, but that streptomycin constitutes the most effective drug. Recent reports indicate that a combination of these powerful drugs is the best. Wagle and Bedarkar obtained five cures in six patients suffering from pneumonic plague with intramuscular streptomycin (0.66 grm. every four hours), anti-plague serum and sulphamerazine.

disease may extend to ten days, and that plague may affect certain of the lower animals as well as man. Ten days is the minimum period that should elapse from the time of departure from an infected place, the date of the last death, or the arrival of a ship or batch of travellers with

cases of plague among them, before granting free pratique.

The eradication of rats from ships requires special measures. Sulphur dioxide may be used in concentration of 2 per cent., either as 3 lb. of roll sulphur or 4 lb. of liquid sulphur dioxide per 1,000 cubic feet. In the Clayton system, which has never been extensively used in British ports, sulphur is burned in a furnace and the gas propelled by fans throughout the ships.

Hydrogen cyanide is being more extensively employed. Under proper supervision it is comparatively safe and has decided advantages over sulphur, as it does not tarnish metals or damage articles. Hydrogen cyanide diffuses slowly. Small amounts which may be absorbed are rapidly evolved and oxidised on exposure to air or during cooking. Hydrogen cyanide may be generated either by pumping liquid HCN from cylinders or by throwing glass ampoules into holds, or from outside by the Glen Liston apparatus. "Discoids," wood pulp discs saturated with ½ oz. HCN, may be used. Calcium cyanide dust (known in the trade as Calcid or Cyanogas) in a dusting apparatus will dislodge rats from deck fittings and lifeboats, or may be blown as a fine powder through a rubber tube behind panellings.

The proprietary article "Zyklon" consists of highly absorbent material saturated with lacrymatory gas. It is supplied in hermetically-sealed

tins and after fumigation may be disposed of as refuse.

The Nocht-Giemsa method of fumigation consists of a mixture of carbon monoxide and carbon dioxide generated from incandescent coke

driven into the ship.

For fumigation the ship is divided into sections each of which is measured by volume. Water-bottles and cabin water-tanks are emptied, moist food removed and mattresses turned on edge. All apertures are sealed. Danger boards are prominently displayed. Ships may be fumigated loaded or unloaded. A plague infected ship should be treated before

unloading.

When plague breaks out in a small village community, as soon as the disease is recognized, measures should be taken to prevent the inhabitants leaving the locality and thus disseminating it. There is little danger of this until the inhabitants become alarmed by a rapid extension of the disease. If possible, after the patients have been isolated in a special hospital, the village should be evacuated for a month. The safest and most thorough form of disinfection is by fire, and in an isolated village prompt burning of the infected houses is the surest method of stamping out the infection. The clothes and bedding of all patients should be burned. The dead should, with as little delay as possible, be buried in deep graves or cremated. Isolated observation camps should be organized, in which "suspects" and "contacts" may be segregated for a time equal at least to the incubation period of the disease. War should be waged against all rats and mice, and their corpses burned. This is specially

important in rat-infested quarters of Eastern towns, bazaars, grain stores,

go-downs, etc.

In an outbreak in a town, it must be borne in mind that plague, once established in human beings, is communicable to others and to rats by the expectoration, and by discharges from the buboes or glandular swellings; and that a plague in rats usually precedes plague in human beings. The main efforts should be directed towards destruction of rats by methods detailed on pp. 282-283. In addition, therefore, to prompt notification of plague patients, a system designed to obtain information on plague in rats should be instituted. Every rat destroyed must be bacteriologically examined.

After death the rat is treated with Flit or soaked in lysol. Smears are made from lymph glands, liver and spleen, and stained by Leishman. Broquet's medium (calcium carbonate 2; glycerine 20; distilled water 80 parts) is a good preservative for fleas and permits isolation of *P. pestis* after six days.

For the detection of plague-infected houses, guinea-pigs, which do not harbour fleas as a rule, are turned loose in warehouses as convenient traps for rat-fleas.

In India the compulsory inspection of all dead bodies before burial has been found a valuable measure for discovering infected houses and

localities.

Destruction of vermin and other measures in anticipation of the introduction of plague bacilli.—The campaign against rats is usually carried on by rat-traps and rat-catchers, and the cautious laying down of poisons such as arsenic, phosphorus, and baryta. As no one method is satisfactory, it is usual to employ several at the same time. The pumping of SO, gas under pressure is useful for warehouses. So long as the sulphurous-acid gas is dry, and not used on damp articles, no damage is done to merchandise. Care has to be taken with damp things, as they may get discoloured.

Where possible, houses and warehouses should be made rat-proofnot an easy measure, considering the burrowing and climbing habits of the rat. Rattus norvegicus can penetrate ordinary lime-mortar or soft brick, but is stopped by cement and concrete. Its burrows may attain a depth of 18 in., but Rattus rattus is not so active in this respect. Simpson recommended that walls should be at least 6 in. thick, when made of hard brick or concrete, and that they should extend to not less than 18 in. below the level of the ground floor, and the latter should be paved with concrete 3 in. thick, covered with ½ in. of cement. All ventilators should be protected with iron gratings, and all openings around wires and pipes cemented. In New Orleans some warehouses are elevated, leaving a clear open space beneath: in others an impervious wall is built around the ground floor, penetrating 2 ft. into the ground. In a third, and a most effective type, the ground floor is laid out in concrete with a protective wall round the edges sinking 2 ft. into the ground. The mooring cables of ships should be shielded in such a way as to prevent egress or ingress of rats, and all gangways should be taken up at night or when not in use. Native food-stores are, as a rule, set out on poles and can be protected from rat-invasion by suitable wooden discs. Sprinkling chloride of lime

in the vicinity of the burrows has a deterrent effect. House improvement as an antiplague measure has been officially adopted by the government in Java since 1914 and, though costly to begin with, has proved economical in the long run. In some districts the principle of voluntary house improvement was adopted. No compulsion was exercised, other than official propaganda. The result is claimed as a complete success. Plague has disappeared and the population is contented. Compulsory inspection, condemnation of houses, spleen puncture after death in suspected cases and isolation of contacts are unpopular measures.

In South Africa rigorous measures have been adopted by the Health Department to prevent the spread of rodent plague; it has endeavoured, apparently with success, to place a gerbille-free belt between the mountain range and the sea. Gangs, working under departmental rodent officers, employ two main methods—poisoning and gassing. The poisoning is effected by dropping strychnine-impregnated grain into gerbille burrows. Near homesteads, a Capex cartridge is lighted, plunged into a burrow and the opening closed with earth. Meyer has shown that methyl bromide, sprayed at the rate of 10 c.c. per burrow-opening, is efficient in controlling burrowing rodents and their fleas. Care, however, must be taken in its application.

Prophylactic measures based on a consideration of the flea fauna.—Should further research prove the inability of Xenopsylla astia to transmit plague, it should be possible to divide a country into potential and non-potential plague zones by a survey of the rat-flea population. The energies of the Sanitary Department can by these means be focused on the danger spots-

Control of DDT and insecticides.—Spraying with water emulsion of DDT of walls and ceilings of farmhouses and other buildings have proved efficient in control of rat fleas. Nicholson and others by dusting with DDT in the holes and haunts of rats have caused the reduction by 80 per cent of the numbers of X. cheopis and other fleas. Hill, by dusting rat runs and hiding places in Georgia with 10 per cent. DDT in pyrophyllite, has shown that a significant reduction occurred in the numbers of X. cheopis and Leptopsylla segnis. Nicholson and Gaines (1950) could not detect any significant degree of recovery on the part of the flea population three months later. Within a week of application of 5 per cent. DDT powder to rat burrows and runs in shops, warehouses in S. Carolina, the fleas were almost completely eliminated from rats. Barnett in Malta places most reliance on reduction by poisoning with zinc phosphide, arsenious oxide, red squill and Antu (see p. 283). The method of prebaiting, followed up by poisoning with baits and poisons of known efficacy is essential. is necessary to change both the bait and poison for "follow-up treatments."

Personal prophylaxis.—All unnecessary visits, either to plague patients or plague neighbourhoods, should be, if possible, prevented. Attendants on the sick ought to take care that the ventilation of the sick-room is thorough, that cubic space is abundant, and that the utmost cleanliness is practised. Nurses must not hang over patients unnecessarily; they must also be careful to seal up and cover any wounds, no matter how trifling, on their own hands. Stools and urine must be disinfected, and hands frequently washed. To obviate risk from wounds

and to prevent the access of fleas, those engaged on plague duties should wear boots and have the legs protected by trousers tied tightly round the ankles or, better, by puttees. Leather gloves are advisable if there is much handling of furniture or of anything likely to abrade the skin. In the interests of public health it is imperative to isolate all cases of

bubonic and septicæmic plague and their contacts.

The attendants on pneumonic cases should provide themselves with masks of muslin, three- or four-fold, changed when at all damp, and also with goggles to protect the eyes. In Mukden a mask of absorbent cottonwool (16 by 12 cm.) enclosed in muslin, and retained in position by a many-tailed gauze bandage, together with goggles, rubbe gloves, and cotton uniform, proved thoroughly effective. Evacuation of the people from insanitary and overcrowded dwellings and their installation in camps where better hygienic conditions can be arranged is imperative. Churches, schools and theatres must be closed. Cordons within the affected area, to limit the infection to a circumscribed portion, may assist. In pneumonic plague epidemics general inoculation with plague vaccine is advisable.

Prophylactic inoculation. Haffkine's inoculation consists essentially in the subcutaneous injection of six-weeks'-old cultures of plague bacilli incubated at 25-30° C. and killed by heat-65° C. for one hour; carbolic acid 0.5 per cent. is then added; up to 4 ml. is injected according to the size and age of the individual. The Indian Plague Commission reported strongly in favour of these inoculations which furnish a protection that lasts about twenty months. Glen Liston stated that in the inoculated the incidence of plague was 8 per 1,000 of the population concerned, whereas it was 34 per 1,000 in the uninoculated in the same communities; the case-mortality in the inoculated was 39.5 per 100 attacked: in the uninoculated 78 per 100. The best results are obtained from a two-months' growth of P. pestis which has been stored about eighteen months. It needs great care in its preparation. Its storage in hermetically sealed bottles should be insisted upon, and every bottle ought to be tested before use. The resulting reaction is sometimes severe. The efficacy of the vaccine depends upon the virulence of the bacilli composing it; cultures made from non-virulent strains are useless. The potency of plague vaccine is enhanced by the incubation of plague cultures at 37° C. in place of 26° C.

So far, Haffkine's prophylactic is the one most frequently used and gives the best results. In 1927, 90,000 inoculations with plague vaccine prepared at the Entebbe laboratories were administered in Uganda. As an index of its efficacy it was noted that amongst 232 cases subsequently attacked by plague

the recovery-rate was 40 per cent.

Those in attendance on plague patients should receive 20 c.c. of Yersin's anti-plague serum, and 3 c.c. of Haffkine's vaccine on the same day; ten days later a second dose of vaccine should be given. Attendants should wear lysol-impregnated gowns fastened at the wrist, ankles and neck, rubber gloves and gum-boots. They should not shave, but they should disinfect themselves and their clothes daily.

better immunity with this living vaccine than that obtained with dead cultures. Otten's method was commenced in 1935 and up to 1939 total injections numbered 9,286,237. Excellent results have been obtained and the present decline in the epidemic is attributed chiefly to this vaccine. The mortality in the vaccinated fell to about 20 per cent. It has been proved possible to obtain a plague strain with combined properties of avirulence and immunogenic power. These two properties do not necessarily coincide. Vincke and Janssens (1944) tested the efficacy of inoculation with the living E.V. vaccine as a protection against virulent strain of P. pestis isolated locally with vaccine doses of 1,000 million to 2,000 organisms, and immunity was conferred in 97 per cent. of the series of guinea-pigs, whereas with Haffkine's vaccine the figure was only 12.5 per cent. Girard reported upon similar results obtained with his living vaccine (E.V. strain) in Madagascar. Passa recorded that in that island cases of plague fell from 3,493 in 1935 to 918 in 1937. Van Hoof used this method extensively in the Belgian Congo.

DESCRIPTION OF THE COMMONER SPECIES OF RATS CONCERNED IN THE SPREAD OF PLAGUE

The spread of plague and epizoötics amongst rats seems to be primarily by the fierce R. norvegicus. The more delicate R. rattus receives its infection from the former, the sewer rat. Both these species are pestigenic. When the rat dies the fleas desert the body and seek a new host; thus if a sewer rat (R. norvegicus) dies in the basement, the fleas attach themselves to the black house rat (R. rattus), and are spread to human beings.

Terms employed.—Rodents which are capable of being infected with plague are divided into pestiferous and pestigenic; thus the common mouse is a pestifer, but is not ordinarily a transmitter. Selvatic (or sylvatic) plague is the plague of the hinterland. In North Africa, for instance, plague of the "bled" of Tunisia has been regarded as selvatic and due to desert rodents; further south in the Sahara a mouse (Psammomys rondairei), though predominant and a very susceptible animal, has hitherto not been affected.

An intimate knowledge of the appearance and habits of the many species of rats is hardly necessary to the tropical specialist: considering the important rôle several species play in the spread of plague he should, however, be able to identify the more domestic varieties. For this purpose the following Table, contributed by M. A. C. Hinton, will be found useful:

Rattus rattus, Linn.—The black rat. Build slender; muzzle sharp; ears large, translucent, cover eyes when folded down; tail usually long, never much shorter than head and body; coarse hair on rump; hind foot (heel to tip of longest toe, without claw) 35—40 mm.; weight of adults rarely more than 8 oz. Indigenous, wild, more or less arboreal in Indo-Burmese countries. In tropics generally dominant domestic rat in houses and ships. The chief domestic races are distinguished as follows:

- A. Back reddish or greyish-brown.
 - a. Under parts pure white or pale lemon. R. r. frugivorus Raf. (=tectorum). Common in Mediterranean region. R. r. kijabius. Uganda.
 - b. Under parts darkened.
 - a¹. Ventral hairs with rusty tips. R. r. rufescens Gray. Common rat of Indian houses.
 - b1. Ventral hairs without rusty tips. R. r. alexandrinus Geoff.

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- B. Back black; under parts dusky or slate-grey. R. r. rattus Linn. Essentially a domestic form which has been evolved in cold temperate countries.
- N.B.—The black rat tends to be brown in the tropics.

The forms frugivorus, alexandrinus, and rattus have now acquired an almost world-wide distribution; frugivorus is the least, rattus the most modified race. These are climbing rats, common on ships; frequent in dwellings in warm countries, and not shunning man; they are of especial importance as plague-carriers; attain sexual maturity early (min. weight sex-mature = 70 grm.); breed throughout the year; gestation about 21 days, but with concurrent lactation about 31 days; litter of from 4 to 11; average litter 5 or 6.

Rattus norvegicus, Berkenhout (=decumanus).—The brown, grey or sewer rat. Robust; muzzle blunt; ears small, opaque; tail noticeably shorter than head and body; fine hairs on rump; hind foot 40 to 45 mm.; weight of adults commonly 17 oz., often much more; colour brown or grey above, silvery below. A melanic form (often confused with R. rattus) quite common.

RAT DESTRUCTION (DERATIZATION)

Terriers may be used, the rats being driven out of their holes by flooding from a watercart. Cats are useful, but they are susceptible to plague. Traps of all description are of value, and rats readily enter a funnel-shaped trap showing a light at the far end. Runs may be made with double closing doors, or gins or nipper traps may be placed in the path of rat-runs. One man can attend to 100 to 200 traps a day. In towns and ports where plague exists, 40 to 50 traps should be set per day per 1,000 inhabitants. Rats which are caught alive must be asphyxiated and then combed for fleas. The flea is placed for twenty-four hours in pure phenol to make it transparent, so that species and sex may be determined. The total number of fleas divided by the number of rats gives the "flea-index."

One of the modern methods of rat destruction is the use of lithographic varnish or "ratsticker." The varnish is spread on a board in a place frequented by rats, with a piece of cheese or other material as a bait. On coming into contact with this substance, the rat becomes hopelessly entangled and its squeals attract other rodents to the rescue, so that they in turn become trapped. Rat traps should not be handled, except with gloves. They may be covered with mud, or anointed with oil of aniseed, which removes the human smell.

Baits.—A good bait is one which differs from food usually found on the premises. In fish shops, meat, cheese or bread should be used. In grain stores, bloaters, cheese, etc. Dry bread is always acceptable, while catmeal and tallow can also be used. It is said in the tropics that tomato is specially tempting.

Poisons.—Squill (red squill) pancakes are made with beef dripping to which has been added 20 per cent. of finely chopped Urginea maritima (red variety). The pancakes are cut into baits each ½-inch square. Various squill preparations are on the market. Squill is mixed with equal parts of milk, and 8 lb. of bread, soaked, for every gallon of solution. The toxic dose for a rat is 1-3 ml. of a liquid extract. Its action on the rat is slow; the first symptoms being excessive purging, thirst, and general discomfort, followed by paralysis and convulsions. Death is hastened by drinking. The ground-up bulbs make the best bait. On the basis that a rat eats one-tenth of its body-weight every 24 hours, each bait should consist of 60 gr. In autumn female rats are especially attracted by these methods. Powdered squill is quite dangerous to handle, and liquid extract is the safest preparation.

Barium carbonate, 1-2 gr. kills a rat. Cats and chickens can stand 10-15 gr., whilst dogs can take 100 gr. This poison drives rats to seek water so that they die in the open. A 10-50 per cent. mixture of barium carbonate with fatty basis (i.e. tallow) forms one of the safest and most effective poisons. "Zelio" paste, or poisoned grain (Bayer), in which the grain is thoroughly soaked, is said to be absolutely tasteless and readily eaten by rats. The bait is set at night and removed in the morning. After touching the poisoned bait the hands should be washed. 1080, is the name of a proprietary preparation which is now being used with great success in the Americas, especially in Panama.

Zinc phosphide, 2½ per cent. in sausage-rusk, or the appropriate bait, is most effective after prebaiting with unpoisoned bait. Highly poisonous to man.

Thallium sulphate is a heavy metal, and is a slowly acting poison for control of rats and field rodents.

Antu (alpha-naphthyl-thiourea) is a light grey powder insoluble in water, highly stable. Toxic especially to sewer rats in concentration of 1-1.5 per cent., less so to Alexandrine and black rats. Can be used as dust on runways or pumped into burrows in a mixture of 20 per cent. Antu, 2 per cent. DDT and 78 per cent. pyrophyllite. Controls rat fleas as well as rats.

Effective, but dangerous to stock.—(a) Strychnine and barium—Battle's yermin killer. (b) Arsenic and barium—"Rough on Rats." (c) Phosphorus—"Extermo," "Rodine," "Farmer's paste," "Roth's paste" and "Sandford's paste." In Hawaii a banana-phosphorus bait is said to be effective. Cyanide preparations are better than trapping or baiting, because they also destroy fleas.

Partly effective but dangerous to man.—The virus of Danysz and similar viruses, which are bacillary in origin, vary very much in lethal effects and have been known to cause "choleraic" symptoms in man. In the tropics they require

frequent subculture.

Cultures.—Danysz virus and other bacilli have been used with the object of causing epizoötics in these rodents, but they have not been successful on the whole. In South Africa similar attempts have been made to extirpate gerbilles, by an organism known as the Tiger River disease (B. monocytogenes) (E. G. Murray), and this has been partially successful.

Various poisons for use in selected cases.—(a) Arsenic, 20 per cent. with meal. (b) Dish of ontmeal mixed with sugar, grated Parmesan cheese, and a small quantity of strychnine. (c) Dish of chicken heads. A pinch of strychnine

should be placed in each neck with a drop of blood.

Toxic gases.—Calcium cyanide, sulphur dioxide, methyl bromide, carbon monoxide (from automobile exhausts) forced into burrows.

GROUND SQUIRREL AND RODENT CONTROL (California and S. Africa)

General measures: (1) poison bait, (2) poisonous gases, (3) trapping, (4) shooting, (5) exclusion, and (6) encouragement of natural enemies (Storer). A poison, 1080, is used for ground squirrels and "prairie dogs"

-1-2 oz. in 100 lb. of grain act best.

Gassing with carbon bisulphide is highly effective. Strychnine-coated barley is made as follows (the bitter taste being delayed by these means):—Barley 16 quarts; strychnine 1 oz.; sodi bicarb 1 oz.; starch paste $\frac{3}{4}$ pint; corn syrup $\frac{1}{4}$ pint; glycerine 1 tablespoonful; saccharine $\frac{1}{10}$ oz. In California and Western U.S.A. the abundance and variety of rodent fleas found in the nests of the burrowing owl (Spectyto cunicularia) suggests that this bird is a host and carrier of plague-infected parasites.

CHAPTER XIII

TULARÆMIA

Synonyms. Deer-fly Fever; Pahvant Valley Plague; Rabbit Fever; Ohara's Disease.

Definition.—Tularæmia is a specific infectious disease of rodents, caused by *Brucella* (*Pasteurella*) tularensis, and is transmitted from these animals to man by the bite of infected blood-sucking insects, or by the handling or dissection of infected jack-rabbits and other rodents. From group agglutination tests it now appears that *Br. tularensis* is closely allied to the *Brucella* group, but has epidemiological relationship to plague, as both are primarily diseases of rodents conveyed to man by biting insects.

Epidemiology and endemiology.—In American endemic areas the disease is most prevalent in the months of June, July, and August, when it is conveyed by a blood-sucking fly, Chrysops discalis, from one infected jack-rabbit to another. In Scandinavia and in Northern Europe most cases occur from July to October; in Southern Europe and Asia Minor from June to August. Tularæmia is a disease of the rural population. particularly field workers, but it has also been recorded among dealers in rabbits who handle infected jack-rabbits, and those who prepare their skins for market. In 1924 Parker and Spencer found that the tick (Dermacentor andersoni) could act as a host and as vector of the disease in man and in rodents, and demonstrated that hereditary transmission takes place in it. They further showed that the rabbit tick (Hæmaphysalis leporis-palustris) acted as a vector from one rodent to another. Olin studied a serious outbreak of 115 cases in Sweden in 1937 which occurred especially among peasant women, who in summer-time go bare-footed and who are stung by numerous mosquitoes, and he considered that these insects may act as vectors. Although in the main an insect-borne disease. it may be water-borne. "Lemming fever" in Norway is tularæmia due to drinking water polluted by bodies and excreta of lemmings. In Montana, U.S.A., streams are similarly contaminated by beavers, and in Wyoming these animals have been found dead in large numbers from Br. tularensis infection. Ingestion tularæmia is contracted by eating insufficiently cooked flesh of an infected animal.

Ætiology.—Brucella tularensis is a small non-motile, Gram-negative organism, measuring $0.8-0.7~\mu$ in length; when stained in the tissues it gives the appearance of being surrounded by a capsule. Though normally occurring as a rod-like structure, it frequently assumes a coccus shape. It stains best in tissue preparations with Giemsa's stain, but in smears from cultures it shows up well with aniline gentian-violet. On account of their small size some of the organisms pass through the coarser bacterial filters.

¹ This organism was at first thought to be a bacterium, then removed to the genus Pasteurella and finally it is classified as a Brucella.

The organism is difficult to cultivate; it will not grow on plain agar or in bouillon, and, until recently, had been cultivated only upon the coagulated yolk of hen's eggs, but Francis succeeded in producing an abundant growth upon serum-glucose-cystine agar. The cystine medium is inoculated with the heart's-blood of the infected animal, or a small piece of the liver or spleen is rubbed on the surface and allowed to remain in contact with the medium. Growth appears about the third day, and flourishes luxuriantly on subcultures without the addition of fresh animal tissue. To ensure the primary growth, it is necessary that a piece of animal tissue be added to the medium. Fermentation of glucose, lævulose, maltose and glycerine occurs, with acid formation.

Composition of custine agar.—Cystine agar consists of beef-infusion agar, having a pH of 7.6, to which 0.02 per cent. of cystine is added, after which it is sterilized for fifteen minutes in a steam sterilizer, and subsequently incubated for twenty-four hours to ensure sterility.

Cultures of Br. tularensis are extraordinarily infectious, and should be handled with great care.

In its serum reactions cross-agglutination occurs in connection with Brucella melitensis and Br. abortus. About 23 per cent. of tularæmia sera do so, and about 35 per cent. of undulant fever sera agglutinate Br. tularensis to some degree. Concentrations of the organism are best obtained from emulsions made from the spleens of infected mice or guinea-pigs.

The organism is pathogenic for guinea-pigs, rabbits, white rats, mice, ground-squirrels (Citellus beecheyi), gophers (Thomomys bottæ), and Macaca monkeys; while brown rats (R. norvegicus), horses, calves, pigs, goats, cats, dogs, fowls and pigeons are found to be refractory. The organism can be transmitted by Chrysops discalis, as well as by the stable-fly Stomoxys calcitrans, the bed-bug, Cimex lectularius, the squirrel-flea, Ceratophyllus acutus, the rabbit-louse, Hæmodipsus ventricosus, and the mouse-louse, Polyplax serratus.

Ticks can also act as vectors—i.e. Dermacentor andersoni, D. variabilis. D. occidentalis, Ixodes ricinus, var. californicus, Banks, and the rabbit tick (Hæmaphysalis leporis-palustris). Four species of mosquito, Aēdes and Theobaldia, have been shown to transmit B. tularensis under experimental conditions. In Sweden Aëdes cinereus does so in nature.

Dermacentor andersoni is particularly important, Br. tularensis being found in the intestinal lumen, in the cells of the gut wall, in the body fluids, and in the fæces. The organism is harboured throughout the winter months and infection is transmitted to the eggs of the tick.

The disease occurs as a natural infection in wild rodents, especially in rats, field mice, hares and rabbits. Burroughs, Holdenfried and others have given a complete list (1945). In the United States: The wandering shrew, grey fox, dog, cat, various ground squirrels (Pirote, Wyoming, Beechey's and Columbian), the chipmunk and the beaver, woodrat, white-footed mouse, meadow mouse and varieties (the Sawatch and Tule), musk-rat and Norwegian rat, the varying hare, the jack-rabbit, blacktailed jack-rabbit, cotton-tail rabbit, sheep and calves. The following birds also: Ruffled grouse, sharp-tailed grouse, sage hen, bobwhite quail, horned owl. In Canada: Richardson ground squirrel, Osgood's whitefooted mouse, Drummond meadow mouse, varying hare and white-tailed jack-rabbit, Franklin's gull. In Sweden: The lemming, varying hare. In Russia: The dog, little ground squirrel, Steppe lemming, water rat, hamster, continental vole, large water vole, house mouse and long-tailed field mouse. In *Turkey*: The continental vole (*Microtus arvicola*), house and harvest mouse. In *Austria*, *Czechoslovakia* and *Poland*: Rabbit and hare. In *Tunisia*: The rabbit, and in *Japan* the local rabbit (*Lepus brachyurus*). Undoubtedly in America the most important reservoir of infection is the jack-rabbit and its cogeners.

Man is extremely likely to contract the disease from animals, consequently laboratory infections are very frequent.

The nasal secretion and the urine of infected mice and rabbits are infective for other animals.

Pathology.—In animals there is usually a fatal septicæmia. The pathological appearances of infected guinea-pigs and rabbits at autopsy much resemble those of plague in the same animals. In an experimentally-infected guinea-pig there is hæmorrhagic ædema at the site of inoculation,



Fig. 50. Tularæmia. Section of liver showing aggregation of Brucella tularensis in hepatic cells.

(After Prof. R. P. Strong.)

with blood-stained peritoneal exudate, and diffusely enlarged spleen, in which characteristic small necrotic foci can be found. Similar lesions may be detected in the liver; on microscopic section of these organs a dense infiltration with polymorphonuclear cells can be found, but the organisms can with difficulty be detected (Fig. 50). In the spleen of the mouse, on the other hand, little or no leucocytic response occurs; and when stained with Twort's light-green neutral-red stain, Br. tularensis can be readily demonstrated in large numbers. In the few recorded fatal cases in man nodules have been found in the lung and spleen.

Symptoms.—The incubation period appears to be from one to ten days. Unrecognized cases of tularæmia are probably common in the endemic areas, for it may occur as a generalized disease without local lesions, or local lesions may be present with secondary lymphadenitis, which may not cause grave constitutional disturbances. As a rule, in

the cases which have been so far recorded, a definite fever is present. The onset is sudden, with headache, backache, and fleeting pains, remarkable lassitude, and pyrexia which may last for three weeks or more; the extreme range of temperature is about 104° F. The pyrexia may subside to normal, or nearly so, from the third to the sixth day. The pains commence at some particular point and persist for two weeks to a month, though localized ones of greater or lesser degree may recur for the succeeding twelve months. Epistaxis and dizziness are common; weakness and lassitude persist for weeks after the pyrexia has subsided and it may be months before normal health is restored. The spleen is not palpable. Typhoidal tularæmia has been observed in about 5 per cent. of cases.

Such is the description of the generalized disease as it is met in man. When infection results from inoculation, the effect may be purely local; an inflamed papule occurs at the site, with secondary lymphadenitis. After the bite of an infected chrysops, or other fly, on some exposed surface of the body, the onset is sudden, with pains and fever. The initial ulcer, which may develop within 48 hours, presents a process of diffuse necrosis with infiltration of the base. Sometimes subcutaneous nodules resembling sporotrichosis appear on the anterior and posterior aspects of the forearm and along the lymphatics between the ulcer and the regional glands. They are firm, movable, tender and 4–10 mm. in diameter. The patient may be prostrated and have to retire to bed; the lymph-glands draining the bitten area subsequently become inflamed and swollen and suppuration may occur. Subcuticular roseolar rashes on the body and arms are sometimes observed in Western America. Nodular and pustular lesions have also been recorded.

Three cases of laboratory infection of tularæmia have been recorded in England. Though the debilitating effect is very marked, only one death, in a series of seven cases reported from Utah, has been recorded, and this took place from apical pneumonia. There is, apparently, a lasting immunity in man. There is no record of a second generalized attack, though, as in Francis himself, a local re-infection may occur.

Infections of the eye and conjunctiva, causing acute conjunctivitis, were recorded by Vail, Lamb, and others. In America, an ocularglandular process is well recognized. The primary lesion is of the conjunctiva and there is a regional lymphadenitis of the head and neck. Severe conjunctivitis results, with chemosis and cedema of the lids and surrounding tissues. There is now little doubt, as pointed out by Herrenschwand (1935), that "Parinaud's conjunctivitis," first described in Paris in 1889, is none other than ocular-glandular tularæmia. Parinaud recognized that it was infectious and that it was associated in some manner with animals. It is characterized by the granular condition of the lids, with chemosis of the conjunctiva, inflammation and enlargement of the pre-auricular lymphatic glands. In 1917 and 1918 Herrenschwand observed two cases in Austrian soldiers, and isolated a bacillus pathogenic to guinea-pigs (undoubtedly Br. tularensis); a small portion of a culture, accidentally dropped into the canthus of the eye, immediately produced typical conjunctivitis.

Diagnosis.—This disease is most readily reproduced by inoculating material from the patient's ulcer, or gland-juice obtained by aspiration, into guinea-pigs, mice, or rabbits, thereby producing generalized tularæmia in these animals, from whose tissues the organism may be isolated on special media. The organisms are rarely present in the blood of human cases. Agglutination tests can readily be performed; the serum of patients suffering from the disease will agglutinate suspensions of the organism in high dilutions but. as pointed out by Ledingham, where cultures of Br. tularensis cannot be obtained, the spleens of infected mice contain the organisms in such large numbers that an emulsion in formalinized citrate solution may be used instead. Agglutination occurs in the second week, reaching its maximum between the fourth and eighth weeks, when there is a gradual fall, but it may persist for eleven years.

It has been ascertained that a cross-immunity frequently co-exists between tularæmia and the undulant fevers. Calder stated, too, that tularæmia serum agglutinates *Proteus OX* 19 in a dilution of 1:80 and over in 13:5 per cent. of cases.

An intradermal test with a suspension of killed organisms has also been introduced.

The differential diagnosis of this condition has to be made from plague and from rat-bite fever. In both cases alike it depends upon the recognition of the respective specific organisms.

Treatment.—The patient should be kept in bed for several weeks after the subsidence of the fever. Convalescence should be prolonged. The inflamed glands should be dressed with a saturated aqueous solution of magnesium sulphate. Incision is inadvisable, unless suppuration is observed.

Streptomycin (see also p. 276) has a wide and intense potency in animals. In contrast to penicillin it has a maximal action on Gram-negative bacteria. Of all the infections of man in which streptomycin has been tried out it has the maximal effect in tularæmia. Intramuscular injections are given at intervals of three to four hours. The benefit is striking and 1 grm. daily for seven days will terminate the disease when of average severity. Out of 67 so treated there were 63 recoveries (Report of Amer. Med. Ass., 1946).

Prophylaxis.—Prevention depends in part upon the avoidance of contact with infected rabbits in the endemic area. The dangers of experimental work with *Br. tularensis* in the laboratory have already been sufficiently emphasized. The prevention of the disease, from the public health point of view, is by no means easy. Sick or dead rabbits must be handled with great caution and rubber gloves must be worn by laboratory workers, marketmen, cooks, etc., in view of their great liability to infection. Cooking destroys the infection, as does also prolonged freezing.

¹ Confirming that P. tularensis is, in fact, Brucella tularensis,

CHAPTER XIV

MELIOIDOSIS

Synonyms. Stanton's Disease; Pneumo-enteritis; Pseudocholera.

Definition.—This is a rare, glanders-like disease occurring in Burma, the Malay States and Ceylon. A few isolated cases have been described elsewhere, including Europe. The name melioidosis was suggested by Stanton and Fletcher in order to describe its close relationship to glanders $(\mu\eta\lambda l_S)$, used by Aristotle for a "distemper of asses" and $\epsilon i\delta_{0S} =$ form). Melioidosis has many resemblances to tularæmia, both as diseases of rodents accidentally attacking man.

Ætiology.—Pfeifferella whitmori (sometimes known as Actinobacillus pseudomallei) closely resembles Pf. mallei; it is a small bacillus about the same size and shape, and occurs in very large numbers in all acute lesions In films stained by Leishman's method, bipolar staining is very common. Acid-fast granules, decolourized by alcohol, were described by Mayer and Finlayson (1944). On culture also it resembles the glanders bacillus very closely, but is more actively motile and liquefies gelatin more rapidly. It grows luxuriantly upon peptone agar, forming a dense wrinkled culture, especially when the medium contains glycerin. A peculiar aromatic odour is given off, though on repeated subcultures this appearance On broth cultures a pellicle is formed. Brown, Duncan and Henry have shown that Pf. whitmori can be distinguished from Pf. mallei by its behaviour on a pertonized medium containing 1 per cent. sodium fumarate. This organism is pathogenic for most laboratory animals; for guinea-pigs, at any rate, the infection is more rapidly fatal than glanders, but in each case, in the male, acute orchitis is produced on intraperitoneal injectionthe so-called Strauss reaction. Penicillin-treated plates are useful for isolation of the organism when other contaminants are present.

Susceptible animals can be infected by scarification, by feeding or by simple application of cultures to the nasal mucosa; a characteristic feature

in infected animals is discharge from the nose and eyes.

The organism is excreted in the urine and fæces of infected laboratory animals, while several cases of natural infection, especially in rats (*Mus griseiventer*, Bonhote), cats and dogs, have been observed. In 1927 the first case was reported in a horse from the Malay States, when the bacillus was isolated from nasal pus.

Pathology.—The lesions vary very considerably. Numerous small pulmonary abscesses, roughly resembling those of miliary tuberculosis, are produced. Nodules which coalesce and break down into abscesses are found in the liver; they somewhat resemble those of portal pyæmia, and have to be distinguished from amæbic abscesses. The organisms have been recovered from the blood, urine, sputum, and fluid from cutaneous vesicles of patients dying from the disease. In laboratory animals, artificially infected, small nodules form in the internal organs.

Symptoms.—The accounts so far published of the symptomatology are meagre. The first cases observed by Stanton in 1917 were suffering from an acute diarrhea, with collapse roughly resembling that of cholera. and it appears that several patients who recovered from the initial intestinal attack died later from a form of septicæmia with pulmonary lesions resembling tuberculosis. During 1921 a few more cases were encountered. with similar symptoms. Only two are known to have recovered. There is usually a high remittent and somewhat irregular pyrexia. Delirium and mania appear to be frequent terminal symptoms. What appears to be a chronic form of the disease is also recognized; in this the lesions are found in the skin and subcutaneous tissues, leading to cutaneous abscesses and collections of pus in the liver, lungs, and spleen. The initial signs may be those of acute parotitis. Five cases occurred in West African soldiers in Burma during 1946 and have been studied by Harries and colleagues (1948). They ranged in severity from a fulminating disease to one of slow suppuration in localized abscesses. A peculiar case has been reported in England (1943) by Grant and Barwell in a soldier who had served in Malaya. A latent period of three years elapsed between possible infection with Pf. whitmori and the onset of clinical manifestations. The case was characterized by parotid swellings, abscesses, osteomyelitis of frontal bone, perispinal abscesses and bronchopneumonia. A second and almost identical case was diagnosed in a British soldier in South Africa in 1944. He had served in Singapore (Mayer and Finlayson) one year and eight months previously. This patient did not react positively to injection of 0.2 ml. of 1:10 dilution of mallein. An afebrile case with cervical adenitis, with ultimate recovery in an Indian artisan is reported by Green and Mankikar (1949). Very few cases have been recognized in women, but in them the brunt of the disease falls upon the bladder and kidneys. The disease is said to be specially common in morphia addicts, but this is probably a coincidence. How man is infected, as a general rule, is still uncertain.

Diagnosis.—This is obviously best carried out by isolation of the bacillus from the fæces, urine, or blood, and differentiation from the glanders bacillus. In acute cases it may be isolated from the blood on the fifth day of the disease (Mirick) and has been obtained from the cerebrospinal fluid (Martin). Stanton and Fletcher found that the blood-serum agglutinated cultures of the organism in high dilution (1 in 2500 to 1 in 3000), a fact which is extremely useful in diagnosis; a titre of 1:80 is significant: 1:160 diagnostic. Differential diagnosis from malaria, typhoid, dysentery, tuberculosis, plague, cholera and even amœbic liver abscess, may have to be established. There are several resemblances to tularæmia, and both are characterized by pyæmic nodules.

Differential diagnosis from glanders is more complicated. Patients infected with *Pf. whitmori* give a positive reaction to *mallein*, whilst horses infected with melioidosis give a negative test. Central chemotaxis and slight tendency to extension of the lesions, characters regarded by McFaydean as peculiar to glanders, are found in melioidosis.

Prognosis.—Most patients die within ten days of the onset; in chronic cases they may be ill for three to eight months or longer.

Treatment.—In the English case reported above sulphadiazine in large doses reduced the activity of the organism, but failed to eradicate the localized foci of infection. Harries (1948) and colleagues recommend sulphamethazine, 2 grm. four-hourly, as effective and safe. All accessible abscesses should be incised and treated locally with injections of penicillin. Autogenous vaccines cause active immunization where there is no rise in titre of agglutinins in the serum. Green and Mankikar (1948) have shown that chloromycetin exerts an inhibitory effect upon Pf. whitmori suggesting that this antibiotic should be used in treatment.

CHAPTER XV

THE UNDULANT FEVERS (BRUCELLOSIS)

Preliminary statement.—Originally the term undulant fever was employed to designate a type of fever, commonly found in Malta and the Mediterranean area generally, which was usually referred to in medical literature as "Malta fever." Experience, however, has shown that several closely allied fevers are to be classified under this heading. These fevers are due to infection by organisms of the genus Brucella. The following varieties of these organisms and their associated fevers are now recognized:

1. Brucella melitensis (formerly known as Micrococcus melitensis) which is originally a parasite of the goat and which is usually conveyed

to man in goat's milk.

2. Brucella abortus (formerly known as Bacillus abortus, Bang) which is originally an infection of the cow, in which it causes abortion. A strain (Brucella suis) also occurs in the pig. The infection appears to be conveyed to man through cow's milk.

Although *Brucella melitensis* infections have more or less a tropical and subtropical distribution, those of the abortus type are found all over the world, wherever epidemic abortion amongst cattle occurs.

I. UNDULANT FEVER (MELITENSIS TYPE)

Synonyms. Febris Undulans; Malta Fever; Mediterranean Fever; Gastric Remittent Fever.

Definition. A disease of low mortality, indefinite duration, and irregular course, undulant fever is the result of infection by a specific germ—Brucella melitensis. In its more typical form it is characterized by a series of febrile attacks, each individual one, after lasting one or more weeks, gradually subsiding into a period of absolute or relative apyrexia, also of uncertain duration. Common and characteristic complications are a rheumatic-like affection of joints, profuse diaphoresis, anæmia, liability to orchitis and neuralgia. Although only occasionally fatal, the disease is a fruitful source of inefficiency and invaliding.

History and geographical distribution.—Formerly confounded with typhoid and malaria, undulant fever has been established as a separate disease by the labours of various observers—Bruce (1887), Hughes, Gipps, Wright, Semple, and Bassett-Smith. Undulant fever appears to be more widely distributed than was formerly thought. It is not confined to Malta, or even to the Mediterranean; it may occur in Italy, France, Spain, the Red Sea littoral, India (Punjab), China, South Africa, Somaliland, West Africa, the West Indies, the Philippines, South America, Mexico and the United States, especially in New Mexico and Texas. Owing to the close relationship between Br. melitensis and Br. abortus, and the clinical resemblance between the two forms of fever they produce in man, it is extremely difficult to state the exact geographical range of each.

¹ Another species of Brucella is found in pigs (Br. branchisepticus)—but there is no reason to believe that it is communicable to man.

Epidemiology and endemiology.—The most susceptible age is between the sixth and the thirtieth year. Length of residence does not influence susceptibility. In Malta the natives suffer as well as visitors, while there, and in other places where the disease is endemic, it occasionally assumes an epidemic character. The period of its greatest prevalence is the season of lowest rainfall, embracing June, July, August and September, the desease differing in this respect from typhoid which, in Malta, is more prevalent during the succeeding months, but a few cases may occur all the year round. This is explained, not only by the greater consumption of goats' milk during the summer months, but also by the fact that, following the birth of the kid in spring, contamination of the milk is more marked. The goats are not necessarily ill, except for their liability to abort. disease tends to occur in particular towns or villages, in particular houses, barracks, hospitals, and rooms, and in particular ships, manifestly originating in limited foci of infection. Certain ships were formerly notorious foci of the disease. All classes were liable: the officer and his family as well as the soldier in barracks or the sailor on shipboard. The organism has been found in mothers' milk, so may presumably be transmitted to sucklings.

It is not correct to assume, as has so often been done, that because of these essential discoveries, undulant fever has been banished entirely from Malta. The cases amongst the British military and naval population dropped from 245 in 1905 to 12 in 1907, but during the years 1929-35, there was a great increase in the number of cases among the civil population. Gatt (1938) reported that among the latter the incidence of the disease increased till 1934, when as many as 7-25 per mille were infected. Among the indigenous inhabitants there is a deep-rooted prejudice against boiling milk, and they are not content unless the goats are actually milked on their doorstep. However, tinned preserved milk is coming rapidly into favour among the poorer inhabitants as an infant food.

Undulant fever is not, generally speaking, transmitted directly from one person to another; that is to say, is not, as a rule, directly communicable from the sick to the healthy. The germ is readily conveyed by inoculation; the prick of a contaminated needle will suffice. Moreover, it is a well-recognized fact that undulant fever is the most easily acquired in the laboratory from handling cultures. An outbreak of 45 cases in a bacteriology class, of which one ended fatally, was reported by Huddleson and Munger (1940) in Ohio. In this case the actual method of infection could not be determined. Living emulsions of the micro-organism should never be handed round for class work; similarly, infection may be conveyed by sucking a thermometer recently used by a patient. A very striking circumstance is that in some hospitals the nurses and attendants in the fever wards are ten times more liable to the disease than people not so employed.

Milk.—Facts point very distinctly to goat's milk as the most important medium. The organism is present in the milk of 10-50 per cent. of Maltese goats, and monkeys were easily infected by feeding them on it. Directly the goat's milk supply to the naval and military hospitals in Malta was stopped the cases of locally-acquired undulant fever practically ceased. Formerly this fever was very common in Gibraltar. The milk supply of the garrison at that time was largely from animals imported from Malta.

Gradually these goats have died out or been got rid of, and no more have been imported. Concurrently with this there has been a marked and proportional reduction of undulant fever cases in the garrison, so that, as a cause of disability, it has now quite disappeared from the records of the British Army and Navy. There is one well-authenticated instance of wholesale infection from this source in the s.s. Joshua Nicholson, which shipped 65 goats in Malta; an epidemic of undulant fever broke out on board, and nearly all those who drank the milk of the goats were attacked.

Cheese.—There is a considerable amount of evidence that undulant fever can be acquired by eating cheese made from the milk of infected goats. Several varieties of cream cheese made in the South of France, and even ripened cheeses such as Camembert, have fallen under suspicion.

Manure.—In the department of Aude near the Pyrenees, infection by handling manure soiled by urine of infected goats and sheep is regarded as possible.

Ætiology.—Brucein 1887 demonstrated the presence in the spleen in undulant fever of a special bacterium—now called Brucella melitensis—and, by a series of experiments, proved that it was the cause of the disease. Unfortunately, as the bacterium occurs only sparsely in the general circulation (unless in the earlier stages, when the temperature is high), to search for it in the blood in the later stages does not aid diagnosis. The organism is present in abundance in the spleen pulp, and also in the lymphatic glands, in which it persists longer than elsewhere, and from both of which it can be recovered by cultivation. Bruce found it in the spleen in ten fatal cases. His results have been confirmed by many other observers. Injections of pure cultures give rise to a similar disease in monkeys and other animals, from whose blood the bacterium can be recovered, cultivated afresh, and injected into other animals, when it will again give rise to the disease. In five recorded instances, inoculation—intentional and accidental—of cultures of the bacterium into man has been followed by the characteristic symptoms after an incubation period of from five to fifteen days.

A variety of this organism, Brucella paramelitensis, which gives different serological reactions from those of the original strain, has been recognized as responsible for those cases of clinical undulant fever in Tunis and Algeria which do not give a high agglutination reaction with cultures of Br. melitensis.

Br. melitensis measures 0.33 μ in diameter. It occurs generally singly, often in pairs, sometimes in fours, but never, unless in culture, in longer chains. It is Gram-negative and readily stained by a watery solution of gentian-violet, and is best cultivated in a $1\frac{1}{2}$ per cent. very feebly alkaline peptonized beef agar; in this medium, some time after inoculation, it appears as minute, clear, pearly specks. After thirty-six hours the cultures become a transparent amber; later they are opaque. No liquefaction occurs in gelatin. The individual colonies are small, round, somewhat raised discs growing to 2–3 mm. in diameter about the ninth day. The optimum temperature for growth is 37° C. In bouillon it may produce a general turbidity. As a rule, the organism cannot be cultivated under anaërobic conditions. Recently, it has been discovered that the vitamin complex known as biotin is essential for its growth. No indol is formed, and the organism does not ferment glucose. Milk and other media are rendered alkaline.

At one time, Br. melitensis was believed to be a delicate organism, but investigations have shown that it can live for a long time in water, in dust, or on the

clothes of patients, and that it is not killed by cold or desiccation. Moreover, it is now known to be excreted in the urine of man in 10 per cent. of convalescent cases, and to occur in great abundance in the milk and urine of apparently healthy Maltese goats (50 per cent.), and probably of some cows. It has also been found in dogs (9 per cent.), sheep and horses. These facts account in part for the great frequency and dissemination of the disease in such insanitary places as Malta, to which place they specially refer.

Br. melitensis can be cultured from the blood-stream during the height of the fever in a considerable proportion of cases. A liver infusion—Staffseth's medium is now commonly employed as selective culture medium. It has occasionally been obtained from the fæces. The serum of undulant fever cases of this and the Br. abortus type, as well as the milk of infected goats, will agglutinate it. The organism has been recovered from the gall-bladder by Eyre. Amongst the smaller laboratory animals the guinea-pig is highly susceptible to inoculation, a minute

intraperitoneal dose causing prolonged infection.

Br. melitensis was stated by Evans, Myer, Shaw, and others to be morphologically, culturally, and serologically similar to Br. abortus. Three strains. melitensis, paramelitensis, and abortus, are separable one from another only by tests of agglutinin absorption. This criterion must be applied to infections in animals and in man in order to determine their ætiology. Cultures of Br. abortus are agglutinated in high dilutions of the serum of patients suffering from melitensis undulant fever.

It is well known that Br. melitensis may produce abortion in goats, though the animals themselves may exhibit no other clinical changes.

In monkeys intramuscular injection produces within three days a rise of temperature and death within three weeks. According to Burnet and Conseil, melitensis is at least a thousand times more pathogenic for these animals than is abortus. Indeed, only enormous doses of abortus will produce any effect at all in small monkeys.

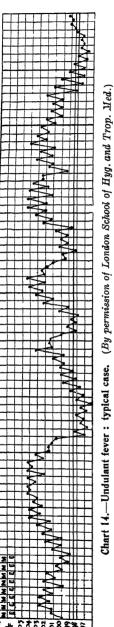
Relationship with Br. abortus.—Intermediate strains of melitensis and abortus have in recent years been isolated from cow's milk, especially in England. In 1940 a strain of Brucella indistinguishable from melitensis was isolated from a farm in Staffordshire, and a further outbreak was reported in October, 1941. Subsequently, after an overall enquiry in twenty counties, another two outbreaks were discovered. In all cases it was found to be associated with true Br. abortus in the same herd.

Eventually it was recognized that organisms exist which, behaving under laboratory tests like Br. melitensis, have not all the features of this organism, especially in regard to pathogenicity. Out of 350 strains of Brucella isolated from milk by R. Cruickshank four were found to be antigenically melitensis, but, from the biochemical aspect, abortus. Strains from S. Italy have been found to behave like abortus antigenically and melitensis biochemically.

Pathology.—The disease has almost no pathological anatomy. The spleen is the only viscus which is distinctly diseased. This is enlarged (average 17 oz.), soft and diffluent; on miscroscopical examination the lymphoid cells are found to be increased. There may be some congestion and even ulceration of the intestinal mucosa, but this is not an essential feature. Other organs show chiefly cloudy swelling, and glomerular nephritis may be present.

Symptoms.—The period of incubation in the naturally-acquired disease is difficult to fix. Cases have occurred as early as six days after arrival, others as late as fourteen and seventeen days after leaving Malta. Some

hold that the disease may remain latent for months. It begins generally



with lassitude and malaise, such as is associated with the incubation of many specific fevers particularly typhoid. There are headache, boneache, anorexia, and so forth. Pain in the eyes. especially on lateral movement, is very characteristic. There may also be a peculiar sensitiveness of the alveolar margins of the jaw and painful movement of the temporo-mandibular joint. At first the patient may go about his work as Gradually the daily task becomes inusual. creasingly irksome, and he takes to bed. Headache may now become intense, and, in addition, the patient suffers from thirst and constipation. At the outset the symptoms, except that there is very rarely diarrhea, resemble those of typhoid, and epistaxis is not uncommon. are no rose spots, however, then or at any subsequent period. There is evidence, in the coated tongue, which looks as if covered with white paint, in the congested pharynx, the anorexia. and the epigastric tenderness, of gastric catarrh: and the occasional cough and harsh, unsatisfactory breathing at the bases of the lungs indicate some degree of bronchitis or of pulmonary congestion. There may also be delirium at night, but as a rule there is insomnia. The fever is usually remittent, the temperature rising about midday (generally about 2 p.m.), falling during the night, and the patient becoming bathed in a profuse perspiration towards morning. The spleen and the liver, but especially the former, are somewhat enlarged and, perhaps, tender. Lumbar pain may be severe.

After a week or two of this type of fever, specially distinguished by pains and perspirations, the tongue begins to clean and the appetite to revive; but, notwithstanding these signs of amendment, the patient still remains listless and liable to headache and constipation. He continues feverish and at times perspires profusely. Gradually, however, although he is anæmic and weak, subjective symptoms become less urgent; he then sleeps well, he has no delirium at night, and can take food, although the body-temperature may still range slightly above the normal. Then once more, and perhaps over and over again, fever with all the former symptoms gradually returns; and now, if it has not

declared itself before, the peculiar fleeting rheumatic-like affection of the joints or fasciæ, so characteristic of the disease, shows itself in a large proportion of cases. One day a knee is hot, swollen, and tender; next day this joint may be well, but another is affected; and so this metastatic, rheumatic-like condition may go on until nearly all the joints of the body have been involved one after the other. Effusions have been reported from which Brucella has been cultured. Purulent synovitis of the costosternal and costochondral joints sometimes occurs. Arthritis and osteitis of the foot with bone atrophy and blurred contours of the joints between the cuneiform and metatarsal bones have been described by Weil. The patient may suffer also from neuralgia in different nerves—intercostal, sciatic, and so on. Orchitis is an occasional early complication, and may be mistaken for testicular mumps. In some cases these complications are severe and characteristic; in others they may be mild, or absent altogether. In this respect the same infinite variety exists as in other specific fevers. severe cases a purpuric condition with bleeding from the gums is occasionally observed. General enlargement of the lymph glands has recently been described.

The most characteristic feature of undulant fever is the peculiar behaviour of the temperature (Chart 14). In a mild case there may be a gradual ladder-like rise through a week or ten days to 103° or 104° F... and then through another week or so a gradual ladder-like fall to normal, the fever, which is of a continued or slightly remitting type, disappearing for good without complication of any sort in about three weeks. Such mild cases are the exception. Usually, after a few days of apyrexia, absolute or relative, the fever wakes up again and runs a similar course, the relapse being in its turn followed by an interval of apyrexia, which is again followed by another relapse; and so on during several months. This is the "undulant" type from which Hughes derived the name he suggested for the disease—febris undulans. A factor of practical importance from the diagnostic point of view is the tendency for the fastigium of the temperature curve to occur towards midday or early afternoon; this feature distinguishes it from typhoid, in which the maximum rise generally occurs towards 6 p.m., or from other long-continued septic fevers, such as that in hepatic abscess, in which this takes place towards night-time.

In cases of another class a continued fever persists for one, two, or more months, with or without the usual rheumatic, sudoral, and other concomitants—the "continued" type of Hughes.

Usually remittent or nearly continued in type, in a proportion of instances (generally paramelitensis infections), the fever exhibits distinct daily intermissions, the swinging temperature chart suggesting sepsis, endocarditis, or malaria. This is the "intermittent" type of Hughes (Chart 15).

In some patients, two to three months may elapse before they are finally rid of the tendency to febrile attacks and characteristic pains and aches. According to Bassett-Smith, the average duration of the disease is four months, but it may last two years. The shortest period is about three weeks.

As in other bacterial diseases, cases of all degrees of severity are met. Bassett-Smith recognized five types:

- (a) Ambulant.—The patients have no symptoms, but are excreting Br. melitensis in their urine and are naturally potential sources of infection. Afterile cases occur with pleurisy and intercostal neuralgia.
- (b) Mild cases.—These last about a fortnight and are apt to be mistaken for paratyphoid.
 - (c) The ordinary type.

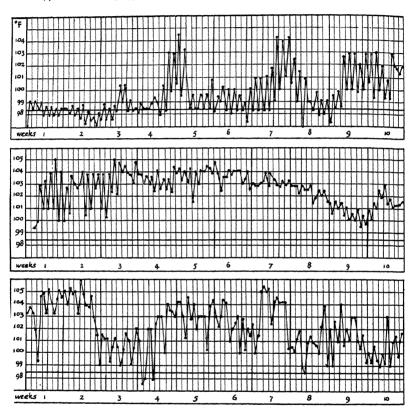


Chart 15.-Various types of temperature chart in undulant fever.

- intermittent type
 remittent type
- (3) irregular type
- (d) The malignant type, with hyperpyrexia and toxemia. This may be fatal, and considerable difficulty may be experienced in making a diagnosis, as in the case reported by Archibald in which death took place on the twenty-seventh day.
- (e) An intermittent type with hectic fever, sweats, and general wasting. This is apt to be mistaken for tuberculosis, and appears to be common in South Africa (Chart 15).

(f) A chronic type has been described with symptoms relating to the central nervous system with headache and nuchal rigidity. In such cases the spinal fluid may exhibit increased pressure.

As a rule, there is a moderate leucopenia (about 6,000 per c. mm.) with an increase of lymphocytes. Sometimes also a slight secondary anæmia is observed.

Surgical Brucellosis.—Hydrarthrosis of a single joint cavity and superficial abscess formation on the chest or abdomen, without generalized fever, may also be produced by Br. melitensis. Cases with arthritis of the hip joint have been described. Spondylitis of the mid-dorsal vertebræ has been recorded by Löffler and Moroni, and also in S. Italy by Molinelli and colleagues; but only in chronic infections. The Editor has seen one such case from Somaliland where, had not the organism been isolated from pus from a skin abscess, this possibility could never have been suspected. Chronic infection resulting in osteomyelitis of the long bones has been recorded.

Complications and sequelæ.—As a rule, by far the most serious consequences of undulant fever are the debility, the emaciation, the profound anæmia, the rheumatic-like pains, the neuralgias, and such sequelæ as abscess, orchitis, mastitis, parotitis and boils. In the male, intermittent hæmorrhages from the urethra are not uncommon. Orchitis is estimated to occur in 4 per cent. of cases. Dixon and Roaf have recorded acute transient attacks of aphasia and, during convalescence, deafness, tinnitus and paræsthesiæ. In women the disease is apt to give rise to ovarian pains, dysmenorrhæa, amenorrhæa and menorrhagia, and to favour abortion and premature labour. The germ may pass into the fætus; children born in such circumstances are weakly.

Complications, such as splenic and hepatic enlargement, enlargement of the mesenteric and cervical glands, suppuration, phlebitis, chorea, various psychoses, arteritis, endocarditis, pericardial effusion and melæna are met occasionally during the long course of the disease. When death occurs it is usually from suddenly developed hyperpyrexia; occasionally it is brought about by exhaustion, by hæmorrhages and purpuric conditions, or by some pulmonary complication such as pneumonia. Fatal gastric and intestinal hæmorrhages have been described on many occasions. In a few instances the fever is a fulminating type, rapidly ending in death from hyperpyrexia.

Neurobrucellosis.—Attention has recently been drawn to nerve complications (1951); these may occur as a complication during the course of the fever, during convalescence, or long after apparent recovery. It may produce symptoms of meningitis, encephalitis, myelitis, radiculitis or neuritis.

A comparatively common sequel is chronic inflammation of the sacroiliac joint.

Diagnosis.—The diagnosis of undulant fever from typhoid is an important practical matter and may be difficult in the early stages. Reliance has to be placed principally on the characteristic temperature

curve, the presence or absence of rose spots, of diarrhea, of joint complications, and of sweats, the locality where and the season in which the disease was contracted, and the agglutination test. There may be considerable hesitancy in differentiating it from pulmonary tuberculosis, especially in the intermittent form, and there are cases of undulant fever with pulmonary signs and symptoms which may resemble that disease. Undulant fever, moreover, may "light up" a quiescent tuberculosis.

An intradermal or "melitene" reaction (Burnet, 1922) has been introduced. For the purpose, 0.2 ml. of a killed broth-culture, containing half a million organisms, is injected into the skin. If the reaction is positive, a red cedematous area results at the site and persists for several days. Adequate controls with broth and cultures of other organisms should be performed in adjacent areas of skin. According to Nattan-Larrier the melitene reaction is best performed by injecting $\frac{1}{10} \cdot \frac{1}{20}$ ml. of the filtrate of a 20 days' broth culture into the skin 4 in. above the elbow. In typical cases the reaction, which consists of a red plaque 4-6 cm. in diameter, becomes positive in six hours and persists for two days. The reaction is positive on the seventh to tenth day of the fever and persists for ten months after recovery. It has been asserted by Wilson and others that, if this reaction is repeated, abscess formation may result; even gangrene of the skin has been observed.

Hæmoculture.—As early as the second day of the disease the organism may be recovered from the blood-stream. For this purpose 5-10 ml. of blood should be drawn off by means of an aseptic syringe and with great precaution distributed into several flasks of broth. The broth should be incubated at least twenty-four hours, or, if necessary, for as long as 26 days, and subcultures made from time to time on trypsin-agar slopes. On the fifth day, on further incubation, minute dewdrop-like colonies should become apparent, and the emulsion should be tested against a specially prepared immune serum in dilutions from 1 in 40 to 1 in 400. It is said that cultures from the blood-clot may sometimes give better results than those from the whole blood. The technique is described by West and Borman (1945). After removal of serum the clot is maccrated and transferred to crystal violet tryptose broth in a screw-capped vial. The medium is adjusted to pH 6.9. The composition of this medium is: Bacto-tryptose 20 grm., bacto-dextrose 1 grm., sodium chloride 5 grm., para-amino-benzoic acid 0.1 grm., crystal violet (0.1 per cent. aqueous solution) 1-4 ml., distilled water 1,000 ml. The cap of the vial should not be tightened. Inoculate at 35° C. under CO₂ tension for 4-7 days. The culture is then streaked on to a solid medium consisting of bacto-tryptose agar containing 1 ml. per litre of 0.1 per cent. aqueous crystal violet. The inoculations are made once each week for three weeks and plates are incubated four days. The suspicious colonies are isolated and preliminary examinations made by slide agglutination tests. By this method cultures have been obtained in specimens which were negative to agglutination tests. The organism may be obtained by splenic puncture, though this method is rarely justifiable.

Isolation from the urine.—This is much more difficult to obtain than from the blood. The urine must be obtained either by catheter or midstream specimen after the fifteenth day of the disease. Every precaution must be taken to prevent contamination, to which *Br. melitensis* is very sensitive.

Agglutination test.—Agglutination, if performed by the macroscopic method and with modern technique, will generally give positive results. There are several important points to remember in connection with this reaction.

¹ The commercial preparation is known as "brucellergen."

Strain of organism employed for agglutination.—The serum, as a rule, contains no agglutinis until after the second week of the disease. It may be necessary to employ several strains of Br. melitensis, as well as cultures of Br. paramelitensis. Titres of agglutination as high as 1 in 6000 have been reported.

As other sera are known to agglutinate the organism in low dilutions, it is recommended that the blood be heated to 56° C. for half an hour before being used for the test, in order to destroy non-specific agglutinins. The occurrence of a pro-agglutinoid zone (or zone of no reaction) may be a source of error, but only in higher dilutions, and it is possibly due to the presence of anti-agglutinins. It is necessary, therefore, to employ a considerable number of dilutions.

The serum of tularemia agglutinates Br. melitensis. A problem of differential diagnosis may arise when a serum agglutinates both Br. tularensis and Br. melitensis in equal titre. This can only be settled from a serological aspect by testing for the absorption of agglutinins.

Complement-fixation test.—No distinct advantage has been reported for this method over the agglutination test. It is, moreover, more complicated. Often the serum is found to be anti-complementary. The technique is identical with that employed for the standard Wassermann test except that melitensis or abortus antigens are used.

After the fever has gone on for several weeks, diagnosis is, of course, easier; in the early stages, on clinical grounds alone and, apart from the agglutination test, it may be, as already stated, almost impossible. Tuberculosis, abscess, empyema, malaria, relapsing fever, acute rheumatism, and all the causes of continued high temperature of a septic type have to be carefully excluded in attempting a diagnosis. The possibility of the concurrence of another infection—typhoid, for example—must not be overlooked.

Prognosis.—As a general rule, in military and naval forces the mortality-rate is low, from 2 to 6 per cent., but in the civilian population it may be considerably higher. Death may occur from hyperpyrexia, heart-failure, or pulmonary complications. Bassett-Smith pointed out that a persistent temperature of 104° F. may indicate a grave prognosis, as may also an intermittent pulse. Alarming symptoms may develop at any stage of the disease, especially in relapses. Though it may be unwise to forecast how long a fever may last, yet, when the pyrexia has subsided for more than ten days, and the patient's tongue is clean and his appetite good, no further relapses may be expected; but there is frequently a short terminal rise of temperature.

In the malignant type the death-rate may be 10 per cent. or more. A persistent temperature of 104° F. and an intermittent pulse are grave, as are also pneumonic complications. The after-effects of the disease are often incapacitating, especially the production of neurasthenia, neuralgia and cardiac weakness. The debility makes the convalescent an easy prey for any intercurrent disease. It is perred by one attack, that, as a general rule, a lasting immunity is conferred by one attack.

Treatment.—Aureomycin and other antibiotics.—Aureomycin in daily doses of 60 mgm. per kg. are well tolerated by man and 3 mgm. per kg.

parenterally or intramuscularly.

Debono in Malta (1949) has proved beyond reasonable doubt that aureomycin cures this fever rapidly within one week. At first in 14 cases the treatment lasted eight days and the average total dose of aureomycin was 16 grm, but a relapse took place in 4, after a period as long as seven weeks on 2 grm daily. Sudden and well-marked elevation of temperature termed "spiking" at the beginning of the treatment was noted in all. He recommends, that in order to effect a final cure, treatment must be extended over a period of twelve to fourteen days at 2 grm. daily—or one capsule every three hours. No serious reactions have been reported.

The biggest series has been reported by Killough and colleagues (1951) in 39 patients in Egypt. Twelve were treated withh cloromycetin (chloramphenicol) in daily doses of 50 mgm. per kg. for a period of twelve days. The total amount was 36 grm. They became afebrile in an average period of 5·1 days. Eleven were given aureomycin in daily and total doses of the same amount, or 50 mgm. per kg. for twelve days. The use of BAL (see p. 872) in conjunction with aureomycin and chloromycetin has been recommended by Renoux and Roux in animals, especially guinea-pigs, and it is suggested that this procedure might be found advantageous in human cases refractory to these antibiotics. Terramycin has been given to 16 patients, in daily doses of 7·5 mgm. per kg. and a total dose of 44 grm. over a period of 11 days. They became afebrile in an average of 3·4 days.

Relapses were comparatively common. No serious toxic effects were noted, but it is clear that terramycin is as good as the other antibiotics in producing excellent clinical response. The effect of sulphonamides is

transient.

The diet at first should consist of milk (in Malta, boiled); later, of broths and eggs and, if necessary, stimulants; but it should be noted that on sulphonamide treatment stimulants should be omitted. Solids must not be freely given during high fever or when the tongue is coated. If appetite is present, ordinary simple food may be taken. Lemonade or lime-juice should be given after a time; not merely as a pleasant, thirst-relieving beverage, but with a view to averting scurvy if the dietary be too restricted over a long period. Feeding must be conducted with the greatest circumspection, avoiding overfeeding on the one hand and a low monotonous diet on the other. The tongue and the appetite are the best guides.

Prophylaxis.—Wherever this fever is prevalent resorts should be avoided by pleasure- and health-seekers during the summer. As a matter of precaution, in the endemic areas the drinking-water and food ought at all seasons to receive special attention. All milk should be avoided, or sterilized by boiling, and food dishes should be washed with boiled water. Laboratory workers must be careful in handling cultures of the bacterium, for the accidental introduction of the organism into the conjunctival sac has sufficed to cause the disease.

The discovery that goat's milk is the principal medium through which

undulant fever is communicated to man has led to very striking and important results. Unfermented cheese is a frequent source of infection and should be forbidden. In Toulon the disease has been traced to "fromage cervelle" made from the milk of sheep and goats.

These facts suffice to indicate the direction preventive measures should take. Infected goats may appear to be in perfect health and may milk

satisfactorily.

The prevalence of infected animals is best determined by cultivating the organism from their blood or milk; failing this, serum reactions (p. 300) and Zammit's test are employed. The latter, which is known as the lacto-reaction, consists in diluting the milk to 1 in 20 and mixing it with a dense emulsion of Br. melitensis or Br. paramelitensis. The mixture is drawn up into the capillary tube and placed in the incubator for twenty-four hours, when any sedimentation present may be detected. It is better to heat the milk first to 56° C. for half an hour.

Zammit and Debono attempted to immunize the Maltese goat by dermal immunization. A filtrate of a broth culture, containing brucella organisms, is sprayed over the mammary region, into the mouth, and 1 ml. is injected intradermally in four places. The treatment is

repeated four times on alternate days.

Prophylatic inoculation.—Nicolle and Conseil conducted some experiments on man which seem to show that it is possible to immunize against undulant fever by subcutaneous injections of killed cultures of the organism, and similar results were obtained by giving 100,000,000 organisms by the mouth on three consecutive days, and again on the fifteenth day. These results were controlled by subsequently injecting cultures of living organisms; the controls in both cases developed undulant fever.

Dubois and Sollier have employed a vaccine of various strains of *melitensis* mixed with two strains of *abortus*. The complete vaccine made up of five strains contains 2,000,000,000 organisms per ml. The first dose is 0.25 ml. or 500,000,000; the second 0.75 ml. or 1,500,000,000; the third 1 ml. or 2,000,000,000. The full course of injections was given to 111 persons engaged in dealing with infected animals, and none of these developed undulant fever.

II. UNDULANT FEVER (ABORTUS TYPE)

Synonym. Abortus Fever.

Definition.—A definite variety of undulant fever in man produced by *Brucella abortus*, the organism of contagious abortion of cattle and swine.

Geographical distribution.—Undulant fever of the abortus type in man has now been reported from the following countries: Italy, Canada, U.S.A., Denmark, Sweden, Germany, Holland, Switzerland, Austria, Poland, Palestine, South Africa, Rhodesia, New Zealand and Australia. In England the number of cases identified as abortus fever is growing yearly, and in 1938 over 140 were recognized and reported. Previous to this, sporadic cases had been reported from time to time and an attempt had been made to ascribe them to occasional drinking of goat's milk. Abortus cases were reported by Byam in 1918, by the Editor

in 1927, and by Bamforth. Since that time the organism (Br. abortus) has been cultivated from the blood, urine and faces in British cases.

Ætiology.—Traum (1914) isolated Brucella from a pig feetus. Br. suis is transmissible to cattle and also to sheep, and Huddleson isolated the organism from the diseased testicle of a dog. Huddleson and Hardy, in Iowa, U.S.A., established that in that State Br. suis is the cause of many cases of abortus fever in man. There are many references to the concurrence of Br. abortus in the lesions of poll evil and of "fistulous withers" in horses. The organism is commonly associated with these lesions, but there is some difference of opinion whether they have not merely migrated to a suitable focus in which the filaria, Onchocerca cervicalis, is located.

In England, the cow is considered the main reservoir of infection. Menton (1937) found no evidence that goats or other animals are infected with Br. melitensis in England, although cows can be artificially infected, and the organism appears in the milk. It has been shown that Br. abortus can be recovered from 6·3 per cent. of cow's milk, and Elkington, Wilson, Cruickshank and others described outbreaks in schools due to consumption of unheated milk infected with Br. abortus.

Since the discovery of the porcine strain of *Br. abortus* (*Br. suis*) the tendency in America is to ascribe human cases to this source. Evidence in U.S.A. is to the effect that infection is acquired by meat packers from direct contact with pig carcases. Doyle found that a small proportion of sows in England is infected.

Differentiation of Brucella abortus from Brucella melitensis.—Br. abortus is usually somewhat larger than Br. melitensis, being from 0.4μ to 0.6μ in thickness, and varying in length from 0.8 μ to 2.5 or even 3 μ . The organism is remarkably pleomorphic; involution forms are unusual. Br. abortus can be isolated from the milk and uterine discharges of infected animals. Normal strains of Br. abortus of bovine origin cannot be grown in primary culture at the ordinary carbon-dioxide tension of the air, but to ensure growth it is necessary to raise the proportion of this gas to 5 per cent. or 10 per cent. by volume. These requirements diminish as the strain is propagated on artificial media. The simplest method of growing this organism is in a Bullock's jar in which cultures have been placed for incubation, adding a sufficient amount of pure carbon dioxide to produce the optimum concentration. In primary growth the colonies develop after inoculation in a zone 10-20 mm. below the medium. This behaviour is taken as evidence that Br. abortus is micro-aërophilic. After continuous subculture the organism can be grown under ordinary conditions. The porcine type, Br. suis, does not show the carbon dioxide growth requirements of the bovine type.

The organism grows best on glucose agar in which 2 per cent. glucose is added to a simple meat-extract agar medium set to reaction of pH 7.4, or in Fildes' medium. On potato slopes of alkaline reaction, differences in the growth character of Br. abortus and other organisms of the group may be found in week-old cultures; the former gives a uniform creamy-yellow growth, while Br. melitensis and Br. paramelitensis yield a greyish-chocolate or even black growth.

The reaction to dyes is important. The bovine abortus type is inhibited by the presence of thionin in suitable concentration, the porcine type by the presence of basic fuchsin, methyl violet, or pyronin. The melitensis type grows in the presence of all four dyes.

The formation of hydrogen sulphide from proteins or aminobodies containing sulphur is one of the most important biochemical reactions. The organism

is grown on Staffseth's liver-infusion agar medium at a reaction of pH 6.6 and, after sowing, a strip of lead-acetate paper is introduced into the tube. After forty-eight hours' incubation a distinct blackening of lead acetate occurs in the second sown with Br. abortus, while Br. melitensis produces no H₂S at all. On serological grounds, by means of the absorption of agglutinin method, the bovine and porcine abortus may be differentiated from the melitensis type.

Br. abortus from cattle is grown best by seeding glycerin-agar slopes with the uterine exudate, and insulating them under a lowered pressure of oxygen, or in the atmosphere of 10 per cent. CO₂. The best method of ascertaining the presence of Br. abortus in milk is by the cultural method. The milk is seeded with a liver extract peptone-agar in a CO₂ atmosphere. Alternatively, 0.5 ml. of the milk may be injected subcutaneously into the hind leg of a guineapig, and the animal killed after three or four weeks; at the post-mortem examination the inguinal and lumbar lymph glands will be slightly enlarged and congested.

For isolation of Br. abortus from human blood, urine or fæces, the optimum for culture is a medium of pH 6.8, a temperature of 37° C., in an atmosphere of CO₂. When first isolated from the blood or the spleen, the organism may fail to show visible growth on the plates until after three days. Minute dewdrop colonies are then seen, which later become opaque, and are 3 mm. in diameter on the tenth day. Evans considered that 1 per cent. of glucose greatly enhances their vigour and that the new growth is obtained when liver is substituted for ordinary infusion-agar. For the first few generations of culture an atmosphere of carbon dioxide must be maintained, though this is unnecessary for later generations. Huddleson and Abell found that the growth of Br. abortus is inhibited by gentian violet, and that this can be used as a means of differentiation from Br. melitensis.

When cultivated from the blood the growth may be exceedingly slow. In one of the Editor's cases Wilson succeeded in demonstrating a growth on the twenty-first day of incubation, and Rainsforth (1933) recorded success after 60 days.

The isolation of *Br. abortus* from the fæces is no easy matter. Amoss and Poston succeeded by employing the following technique: a stool suspension is heated with an immune serum and clumps any organisms present in the sediment, which is then seeded into Teague's medium. Two plates are incubated in an atmosphere of air and two in a CO₂ atmosphere.

Br. abortus in cattle.—This organism produces abortion in otherwise healthy cows by causing inflammation of the uterine mucous membranes, of the fœtal membranes, and of the fœtus itself. The infection has become very prevalent in highly bred cattle herds when stable fed, both in England and in the United States.

The organisms occur first in the vaginal discharges as well as in the exudate from the uterus, while they are excreted in the milk of infected cows for many weeks and even months, so that Br. abortus is frequently found in commercial milk. In Washington 14 per cent. has been found infected: in Chicago 30 per cent., and in Dresden 32 per cent. When injected into guinea-pigs the infected milk produces small tubercle-like foci in the lungs, liver, and kidneys, and swelling of the spleen, which takes about seven weeks to develop. Sheep and pigs are less susceptible than cows. The symptoms of the affected cow are the escape of varying amounts of greyish-brown mucous discharge from the mucous membranes of the uterus and the chorion. It also affects the udders and probably spreads via the lymphatic channels. When a pregnant cow is infected the fectus is expelled within eight to fourteen days. The fectus itself shows infiltration of the subcutaneous and intramuscular tissues with Br. abortus; the calves are born covered with a purulent exudate and the chorion is converted

into a leather-like substance, with buckling and wrinkling of the intercotyledonous parts of the membrane.

Apparently the bull may play an active part in conveying the infection, as the organisms have been found repeatedly in its genital organs.

The commonest time for abortion in cattle is from the fifth to the seventh

month, and the incubation period lasts from one to thirty-three weeks.

When introduced into a fresh herd the disease usually spreads rapidly and assumes epidemic proportions; then it passes into an endemic state in which it remains for years. As a rule, the uterus frees itself quickly from the infection and Br. abortus is to be found in the udder, and also in the supramammary and pelvic lymph glands, where it persists. From the udder the organism is excreted into the milk, and so it comes about that 34 per cent. of cows which give a positive agglutination reaction excrete Br. abortus in the milk, and may continue to do so for three years.

Under experimental conditions abortion may be produced in goats, guineapigs, rabbits, rats, and mice, though rarely fatal. Guineapigs may be infected by rubbing cultures on to the depilated skin of the abdomen, and when these animals are thus infected artificially, they develop lesions simulating tuberculosis.

Pathology.—This is the same as in *Br. melitensis* fever. Occasionally, abscess of the spleen is observed. There is a general reticulo-endothelial hyperplasia of the lymph glands. Meningo-encephalitis with greyish-white tuberculations is reported in *Br. suis* infections in America.

Diagnosis of epidemic abortion in cattle.—The diagnosis of this infection in cows is made by serum agglutination, which takes place in a titre of 1 in 100 to 1 in 10,000, and the agglutinins can also be proved to be present in the milk of infected cows. For this purpose Bevan introduced the "abortoscope," which consists of a tube containing a standardized suspension of Br. abortus, closed by a cork to which is attached a double loop of thin wire coated with sterile paraffin. On the back of the tube is pasted a label marked "infected." Before use the suspension is thoroughly shaken up, and one loopful of blood from the animal to be tested is taken up in the wire, which is then returned to the tube and thoroughly shaken to mix the blood with the suspension. The apparatus is then stood upright at room temperature so that in infected cases the suspension and the blood-cells settle down to the bottom of the tube, leaving a clear supernatant fluid through which the sign "infected" can be read.

Generally speaking, in cows no attention is paid to an agglutination of a titre less than 1 in 50 in the serum. In a pregnant infected animal the titre gradually rises prior to abortion from 1 in 200 to 1 in 1,000, while a persistent figure of 1 in 400, or over, indicates an udder infection.

The intradermal test or the abortin reaction in cattle.—This test, on the same lines as the tuberculin test, was introduced by MacFaydean and Stockman in 1909 in an attempt to introduce one based upon the hypersensitiveness of infected cows. Holtun (1928) described a double intradermal test in which 0.2 c.c. of a 5 per cent. phenolized suspension of Br. abortus, heated to 65° C. for thirty minutes, is twice inoculated into the same site at an interval of forty-eight hours, when the maximum infiltration of the skin is attained at that time.

ABORTUS INFECTION IN MAN

Diagnosis.—The agglutination test in abortus infections is much the same as in melitensis. An agglutination of 1 in 10 to 1 in 80, in the absence of clinical symptoms, indicates a past infection, while a titre of 1 in 100 or over, in the absence of clinical symptoms, probably indicates a latent

infection; a titre of 1 in 100, or over, in the presence of pyrexia and other symptoms of disease, may be considered as diagnostic of active infection with Br. abortus.

The agglutination test is best performed by the macroscopic method. A practical method of making a diagnosis by the agglutination test is by means of the "glutoscope," an apparatus devised by Bevan on the same lines as the abortoscope.

The intradermal test, or "abortin" reaction, is as useful in the diagnosis of abortus infection in man as is the parallel test in melitensis, and is

performed in the same manner (see p. 300).

Diagnosis by blood-culture is the same as for Br. melitensis, and is successful in about 16 per cent. of cases; (see p. 300). A certain amount of assistance may be obtained from the leucocyte count. There is usually a slight leucopenia with a relative increase in the lymphocytes. The average in seven cases of abortus infection under the Editor's care was leucocytes 6,800, with polymorphonuclears 43 per cent. and lymphocytes 48 per cent.

Symptoms.—Cohen divided abortus fever into five types: (1) the classical undulant; (2) the arthritic; (3) the abdominal; (4) the genital, of which orchitis is the chief feature; and (5) the "catarrhal jaundice" type. It is doubtful whether there are any signs or symptoms sufficiently obvious to enable a differential diagnosis between abortus and melitensis

to be made from the clinical aspect alone.

On the whole, abortus infections run a much shorter course than those of melitensis. Some cases may be so mild that no obvious clinical signs are produced beyond the characteristic pyrexia. Atypical cases show slight fever, headache, listlessness, sometimes abdominal pain, sore throat and nocturnal sweating. As a general rule, however, prolonged pyrexial cases lasting many months, as in melitensis fever, are not common. On the other hand, abortus infections may be remarkably persistent over a year or more, but continued fever of over three months' duration is rare, though cases with multiple rigors and the characteristic undulating febrile curves have been recorded. Some of the most severe clinical cases seen in England have been the result of infections contracted in the laboratory.

The spleen may be palpable as in *melitensis* infections, but is by no means invariably so. The premonitory signs of *abortus* fever are important; the infection may commence with pain behind the eyes and in the alveolar margins of the mouth. Unilateral or bilateral orchitis has been noted. There is usually an initial rigor which is followed by

headaches, profuse sweats, and arthritic pains.

Abortion.—The great majority of pregnant women suffering from this disease do not abort, but the organism has been obtained from the vaginal contents in one such case. In Champney's series of 616 cases abortion

occurred once only.

Hæmorrhage is somewhat unusual. It was noted in 5 per cent. of cases collected by Dalrymple-Champneys. Epistaxis was the commonest manifestation, but melæna, hæmoptysis, hæmatemesis, hæmaturia, menorrhagia, and bleeding from the gums may occur. Robinson (1938)

has reported one in which continuous oozing from the mouth and gums, associated with purpura, almost proved fatal.

Rash.—A papular or urticarial rash has been described, but occurs very rarely (Champneys).

Meningism is uncommon. There is stiffness of the neck, tremor of hands, slurring of speech, Kernig's sign and increased pressure of the cerebro-spinal fluid. Meningitis has occasionally been reported and the cerebro-spinal fluid may show increase in albumin and sugar content, but usually nervous symptoms are transient. One fatal case of meningoencephalitis due to Br. suis has been described in the Mayo Clinic (1932).

Cases of meningo-encephalo-myelo-radiculitis have been described. It is emphasized that the diagnosis of brucellosis should be thought of in cases of chronic ill-health where there are recurring neurological symptoms of short duration with identical or diverse localizations.

Mild and chronic cases.—Alice C. Evans noted that in the United States chronic brucellosis is often characterized by vague symptoms—weakness, nervousness, insomnia, depression and irritability—and that in half the cases the agglutination reaction was negative. She therefore suspected this disease in cases of chronic ill-health in endemic areas. Mild or masked cases with headache are also recorded. In these, ascertainable signs are absent, but small rises to 99° and 100° F. occur in a four-hourly chart, whilst usually a low-grade agglutination with abortus in a titre of 1 in 20 can be demonstrated. Kyger (1948), in chronic infections, has described symptoms resembling disseminated sclerosis.

Jaundice.—A form resembling infective hepatitis has been described.

Localizing symptoms.—Usually the arthritic pain and peri-arthritic effusions which are so characteristic a feature of melitensis infections are not so prominent. It is, however, necessary to refer to two instances of isolated joint affections which the Editor has seen. In both, the shoulder-joint was affected, apparently due to localized abortus infection. Localized abscesses, and even fixation abscesses in bone, due to Br. abortus, have been reported, and constitute the condition known as "surgical brucellosis," as described by Edwards (1937). In America, also, osteomyelitis of long bones, including those of the wrist, and rarefying osteitis of the metatarsals, are recognized. Vertebral lesions resembling spondylitis in Br. suis infection have been described by Bishop (1939).

Treatment.—Aureomycin has been reported by Long and colleagues (1948) to have a curative action on this type of undulant fever whilst results in a case of fever due to Br. suis with daily oral doses of 10-60 mgm. per kg. have been favourable. To avoid Herxheimer reactions the total daily dose for the first 2-3 days should not exceed 250-500 mgms. Spink and colleagues (1948) have reported favourable results in 16 patients. The doses were 0·1 grm. in four divided doses on the first day, 0·6 grm. on the second, 1·6 grm. on the third, and 2·0 grm. daily from the fourth to tenth. Prompt improvement occurred and blood cultures were sterile. In some there was a rise of temperature, fall of blood pressure and tachycardia after the initial dose.

Molinelli (1950) and colleagues have now epitomized the results of aureomycin treatment. That it has a remarkable and immediate effect there can be no doubt when administered orally or parenterally. In the ordinary clinical type oral treatment must be continued for at least thirty days to a total of 70 grm. or even more. In serious cases continuous oral and intravenous therapy is advisable till a total of 50 grm. of the antibiotic has been given. When given intravenously the total dose should be 15 grm. spread over a period of at least twenty days.

Prophylaxis.—The prophylaxis of abortus infection in man is mainly bound up in the very difficult subject of the treatment and prevention of this disease in cattle, for the infection is undoubtedly contracted by drinking infected cows' milk by an individual susceptible to the disease. In herds of dairy cows, many carriers of the infection exist. There is a tendency for the organism to become located in the udder. Prophylactic inoculation and immunization of cattle by employing live cultures of Br. abortus has been extensively practised. In 1906 Bang reported that a certain amount of protection could be conferred upon animals by the intravenous injection of living cultures of Br. abortus some weeks before copulation, and this method was more extensively applied by Stockman in 1914 to non-pregnant cattle. In recent years a living strain of Br. abortus of low virulence has been employed in the immunization of cattle in America and England. These do not set up disease in cattle or render them infectious, and the organisms are not excreted in the milk. It is obvious that the remedy lies in the sterilization of abortusinfected milk, and this can be done by boiling or by pasteurization; thirty minutes at 140-145° F. will destroy the organism.

Since it was reported by Gilbert and Coleman that in 11 cases of human infection in Iowa the source had been traced to association with infected hogs, prophylactic measures have been taken in America in that direction

and on the same lines.

CHAPTER XVI

ENTERIC FEVERS (AND BACTERIUM COLI INFECTIONS)

The enteric group of fevers includes typhoid fever, due to Salmonella typhi, and paratyphoid fevers, due mainly to Salmonella paratyphi-A and S. paratyphi-B. Paratyphoid-C fever has a somewhat different symptomatology (see p. 817). These organisms belong to what is now known as the Salmonella group, and the fevers caused by them were classified during the 1914–1918 war as "enterica."

Geographical distribution.—Besides being the scourge of the young European in India, enteric is common enough in Japan, in China, in Cochin-China, in the Philippines, in Malaya, in Mauritius, in West and South Africa, in Algeria, and, in fact, wherever it has been properly sought. Thanks to protective inoculation with the triple vaccine (T.A.B.) and to sanitary measures, enteric fever during the 1914–1918 war was no longer the chief disease in our armies and from 1939–1945 these fevers no longer were a menace.

Prevalence.—Enteric fever is prevalent among young soldiers and recently-arrived civilians in the East, but, fortunately, liability to infection decreases with length of residence, owing apparently to acquired immunity. The well-known immunity of native races to typhoid is probably due either to mild attacks of the disease in childhood or to the immunizing effect of living in constant contact with typhoid infection. In insanitary native cities—Chinese, for example—where the European would almost surely contract typhoid, the natives have acquired a high degree of immunity. The typhoid and paratyphoid infections among Europeans in the tropics appear to be more virulent, and to cause a death-rate twice as heavy as that commonly observed in England. According to English statistics, the death-rate is given as about 1 in 8 attacked, but in India the death-rate was stated to be rather over 1 in 3.

Up to the early days of this century, typhoid in India used to kill more European soldiers than did cholera. Enteric fevers are apt to occur in camps in localities previously unoccupied by man. This has long been noted in India, while in Australia¹ typhoid has occurred in the back country many hundreds of miles from human habitations.

Epidemiology and endemiology.—The essential factor in the propagation of enteric fevers in the tropics, as in temperate climates, is the individual who is passing enteric bacilli in his urine or fæces, or in both. He may be in the acute or the convalescent stage, or a "carrier." Three kinds of enteric carriers are mentioned by writers on this subject:

(a) The acute carrier, who passes enteric bacilli in the excreta for a short period after an attack of enteric fever. (b) The chronic carrier, who continues to pass enteric bacilli in the excreta for years, possibly permanently. Chronic carriers are more often women than men. The gall-bladder being the seat of a chronic infection, the carrier may be the victim of

¹ Enteric infections have recently been found frequent in Polynesia, especially in Fiji.

gall-stones and cholecystitis. (c) The passive carrier is one who continues to pass enteric bacilli in the fæces without having actually suffered from enteric fever.

The enteric carrier is a danger to the community, the degree of danger depending to some extent on his personal hygiene, but much more on the sanitary condition of the locality. Under an efficient water-carriage system of sewage disposal there is a minimum risk. Where the conservancy system—i.e. the dry closet—is employed, as in the tropics generally, the risk of infection is great. The modes of infection are: (1) directly from the infected person (patient or carrier) to the susceptible; (2) indirectly through water supply; and (3) indirectly by fly-carriage and contamination of food.

S. typhi is practically world-wide. Paratyphoid-A fever is the most common form in the East (India), paratyphoid-B fever in Europe. During the 1914–1918 war the majority of enteric infections in France were paratyphoid-B, and the most extensive epidemic in the British and French troops was on the Gallipoli peninsula in 1915. But, relatively to former campaigns, cases of typhoid were few, the armies being almost completely protected by antityphoid inoculation. In the earlier part paratyphoid-B was the prevailing infection, while in the later phases the cases were almost exclusively paratyphoid-A. Paratyphoid-C fever, which resembles the fevers caused by S. ærtrycke and S. suipestifer, is widespread in British Guiana, but elsewhere has probably not the epidemiological importance of the other three (Giglioli).

Etiology.—Description of organisms.—Salmonella typhi is a Gram-negative motile rod, $2-4 \mu$ in length and 0.5μ in thickness. It is provided with numerous peritrichous flagella, and is very active when grown on artificial media. On these it thrives well, with growth resembling that of Bacterium (Escherichia) coli, but less dense. In its biochemical reactions it differs considerably from that organism, and produces acid without gas-formation in maltose, glucose, and mannite, but causes no change in lactose, saccharose, and dulcite. It produces slight acidity No indol is produced in peptone water (see Table VII, in milk without clotting. p. 473). A method of identifying strains of S. typhi has been introduced by the discovery by Craigie and Yen of the type-specific typhoid Vi bacteriophages. By this technique it is possible to divide typhoid bacilli into a number of well-defined types. The phage type of a strain is a permanent character and the typing of the typhoid bacterium by these means gives reliable results. The paratyphoid bacilli A, B, and C resemble in their general morphological characters and staining reactions S. typhi, but differ from it in their biochemical and immunity reactions. They also, like S. typhi, are non-lactosefermenters, but produce acid and gas in glucose, mannite, maltose, and dulcite, though they do not affect saccharose nor form indol in peptone water. Paratyphoid-A bacterium is weaker in fermentative power than B, and it produces permanent acidity in litmus milk, whilst B first produces acid, returning later to a permanent alkaline reaction. Their immunity reactions are also quite specific. Paratyphoid-C bacillus (S. paratyphi-C) differs from B in its immunity reactions, and some bacteriologists might prefer to regard it as a serological race of S. suipestifer.

The portal of entry of the enteric bacilli into the tissues of their host appears to be the lymphoid masses forming the Peyer's patches and solitary follicles of the ileum. Here they cause a hyperplasia of the lymphoid tissues, followed

at a later stage, in severe cases, by necrosis, sloughing and ulceration. The bacilli pass on to the lymphatic glands of the mesentery and posterior abdomen, which become enlarged. Finally, they enter the blood-stream. The period of bacillæmia coincides with the early febrile stage of the disease, and hæmoculture is successful in the majority of cases in which it is undertaken sufficiently early—i.e. while the temperature is still rising, or when it is continued without marked remissions. It is seldom successful after the first marked morning remission, especially in paratyphoid fever, or after lysis has commenced. The duration of bacillæmia varies greatly, depending on the severity of the case and duration of the pyrexia. It is, on an average, longer in typhoid than in the paratyphoid fevers. It is important, therefore, in the diagnosis of enteric fever, to set about hæmoculture as early as possible; every day's delay diminishes the chance of success.

Alternately, it has been suggested that in enteric infections the invading organisms enter the blood-stream first (possibly through the tonsils), and that the intestinal lesions are secondary to the bacillæmia.

Although bacilli are eliminated in the fæces and urine, they cannot always be isolated from the excreta, even on repeated examinations, though the modern use of selective media has increased the proportion of successful results.

Pathology.—The most striking lesions found post mortem (in addition to the tissue changes common to all continued fevers) are: ulceration of the intestine, especially the Peyer's patches and solitary follicles in the ileum and jejunum; enlargement and congestion of the abdominal lymphatics; and enlargement and congestion of the spleen.

The most notable differences in the post-mortem appearances between typhoid and the paratyphoid fevers are: in paratyphoid fevers the intestines more frequently show no change, though they may be acutely inflamed throughout their length, the lymphatic tissue escaping; and in paratyphoid fevers ulceration of the large intestine is relatively more frequent. Paratyphoid-C is in many instances a septicæmia, and deep metastatic abscesses due to this organism are described by Giglioli.

Post-mortem bacteriology.—The causative organism in enteric fevers may be recovered post mortem from the intestinal lesions, enlarged abdominal lymphatics, the spleen, the gall-bladder, the heart's blood, and other tissues.

Symptoms.—The usual *incubation period* for all the enteric infections is about fourteen days, but it may be shorter than seven or longer than twenty-one days.

There is a wide range in the severity of the infections, and one clinical description cannot apply equally to all cases, from the mildest to the most severe. The variation is, however, more in the degree than in the nature of the clinical manifestations. After all that has been written, especially during the 1914–1918 war, on "atypical" enteric fever, this group remains, whether in inoculated or uninoculated patients, remarkably true to one type—which may be termed the "enteric type."

The typical onset is a gradual one, but it may, especially in paratyphoid fever, be sudden, with a shiver or even a rigor. Headache is the most constant early symptom, and is usually accompanied by malaise, anorexia, pains throughout the body and limbs, and insomnia. The tongue is coated, the mouth dry and uncomfortable, and the patient thirsty. There is a characteristic moist facies with cheek-flush, and general apathy. These symptoms vary greatly, and in the mildest cases may pass

undetected. Epistaxis is more common in typhoid than in paratyphoid. There may be pain or general uneasiness in the abdomen, but in mild paratyphoids the patient in many cases does not refer to that region. There may be diarrhea from the commencement, or diarrhea followed in a few days by constipation, or the patient may have obstinate constipation from the beginning. The temperature is invariably raised. It may mount step-ladder-like during the first week, or it may rise suddenly, to reach its highest point in the first 24–28 hours, and, after a period of continued fever, begin to remit in the morning and terminate by lysis.

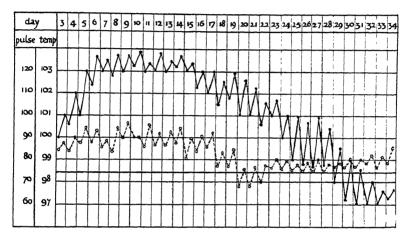


Chart. 16.—Typhold fever, with graph of pulse-rate, S. Typhi isolated from blood 6th day; rose spots present and spleen palpable 9th day. (Garrow.)

A highly characteristic feature of all the enteric infections is the pulse, which is usually soft, often dicrotic, and relatively slow (Charts 16-18).

On physical examination, the abdomen may be found more or less distended, as in severe typhoid, or there may be little or no distension, as in the majority of paratyphoids. Splenic enlargement is practically constant, the organ usually being large enough, at some stages of the illness, for its lower pole to be palpable below the left costal margin. It may be felt in some cases on the second or third day, if the patient comes under observation so early, or not until the second or third week, or even later. In some cases it becomes palpable for the first time only after the temperature has become normal. Usually about the seventh to the tenth day, but it may be earlier or much later, "rose spots" appear. These vary considerably in number, size, shape, general characters and distribution. There may be only two or three on the abdomen, or the body and limbs may be covered, from the soles of the feet to the scalp. They are of a pale-rose colour, slightly-raised, round or lenticular, and fade on pressure. The more profuse eruptions occur in paratyphoid fever, especially paratyphoid-A. When the eruption is not of this profuse type its distribution is characteristic: 90 per cent. or more of it is on

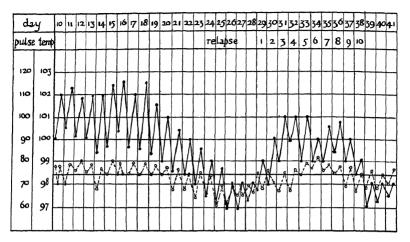


Chart 17.—Paratyphoid-A fever, with graph of pulse-rate. S. paratyphi B isolated from blood 10th day, and S. paratyphi A on 31st day. (Garrow.)

the trunk, between the levels of the iliac crests and the nipples. The patient usually coughs and has a certain degree of bronchitis. Certain features of S. typhi infections, as they occur in Chinese, have been remarked upon by Wilkinson, Snapper and others. Multiple rigors are by no means uncommon. Hepatitis typhosa and jaundice, due to empyema of the gall-bladder, are frequent, whilst hæmorrhage, perforation and phlebitis are rare. The organism has been recovered from the cerebrospinal fluid in patients with meningeal symptoms. Atrophy of the skin and alopecia are common sequelæ, but a most dangerous complication is the lighting-up of long-standing pulmonary tuberculosis.

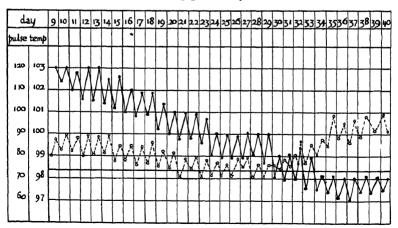


Chart 18.—Paratyphoid-B fever, with graph of pulse-rate. S. paratyphi B isolated from blood 9th day. (Garrow.)

Typhoid osteomyelitis of the long bones, especially the tibia, or of the spine is perhaps a more common sequel in the tropics than elsewhere.

DIAGNOSIS

Clinical diagnosis.—In the literature of enteric there is frequent reference to mild, atypical, abortive, and clinically unrecognizable forms; and it appears to have become the custom to leave the question of diagnosis to the laboratory. This was particularly so during the 1914-18 war, both at home and abroad, and it is greatly to be deprecated, because careful and repeated clinical scrutiny of these cases is more than ever necessary. In Garrow's opinion, the great majority can be correctly diagnosed clinically. While laboratory methods of diagnosis in the enteric group are undoubtedly important, undue value has been attached to certain bacteriological and serological findings, even to the extent of creating new clinical types of the disease to correspond to them. Far from being protean in their clinical manifestations, the enteric fevers are remarkably constant and true to type. The cardinal signs are five: (1) pvrexia of remittent type ending by lysis; (2) low pulse-temperature ratio; (3) characteristic toxemia; (4) splenic enlargement; (5) eruption of rose spots. It is not pretended that this list exhausts the diagnostic signs and symptoms; but a consideration of these five signs will, in the great majority even of the milder cases, lead to correct diagnosis.

(1) Pyrexia.—Continued pyrexia of remittent type, ending by lysis, may be regarded as a feature of every case of acute enteric fever (typhoid or paratyphoid). The pyrexia may be high or low, long or short, with remissions great or small. The onset of pyrexia may be gradual or sudden, and lysis may be slow or rapid, thus giving a great variety of temperature charts within the type; but there is no good evidence to show that the fever ever departs from this type. Cases presenting the following features

certainly should not be regarded as enteric:

(a) Temperature is normal or subnormal throughout the entire illness ("apyrexial type of enteric").

(b) Temperature reaches normal or subnormal at some period of the twenty-four hours on every day of the illness ("intermittent type of enteric").

(c) Temperature shows perfect tertian or quartan periodicity through-

out (" malarial type of enteric").

(d) Temperature shows a series of short relapses of one to three days' duration, occurring at intervals of a few days ("trench-fever type of enteric").

(e) The temperature ends by a genuine crisis.

Examples of all these so-called "types of enteric fever" will be found in the literature, the erroneous diagnosis having been based upon the unwarrantable bacteriological or serological finding.

(2) Low pulse-temperature ratio.—One of the most valuable diagnostic points is the slowness of the pulse in relation to the pyrexia. The normal pulse-temperature ratio may be tabulated as follows:

Pulse . . 50 60 70 80 90 100 110 120 130 140 Temperature . 96° 97° 98° 99° 100° 101° 102° 103° 104° 105°

In enteric fever the pulse is, as a rule, 20, 30 or 40 beats per minute slower than thus indicated. For example, it is common to find an enteric patient with a temperature ranging about 103° to 104° F. and a pulse of 90 beats per minute, or it may be even slower. If the pulse is recorded graphically in red ink alongside the temperature curve in black. a very striking clinical feature of great diagnostic significance is clearly

(3) Characteristic toxæmia.—There is something very characteristic in the general appearance, facies, and decubitus of the enteric-fever patient. His disease may in many cases be confidently diagnosed by a glance. He has a dull, heavy, toxin-laden appearance in the early acute stage. with a moist face and flushed cheeks. The experienced clinician at once recognizes the difference between this and the toxemia of, say, malaria or relapsing fever. In the mildest paratyphoid infections there is little or nothing of this toxic appearance, whilst some infections other than enteric are accompanied by a general toxemia closely resembling it. Nevertheless, this sign, to the experienced physician, when taken in conjunction with the others, is of diagnostic significance.

(4) Splenic enlargement.—As some degree of splenomegaly is practically invariable, this sign is of considerable value in making a diagnosis. Unlike the majority of tropical splenomegalies from other causes (malaria, kalaazar, etc.), the enlargement is acute, so that, even when superadded to a spleen already enlarged from malaria, it has certain exceptional features of diagnostic significance. For example, the acutely enlarged spleen of enteric is tender. On palpation, the edge is seldom more than two fingers' breadth below the costal margin, often not so much; and the enlargement is of comparatively short duration. The spleen may only be palpable for two or three days, and then recede. It may become palpable as early as the second or third day of fever, or not till the second or third week, and it may remain enlarged long into convalescence.

(5) Rose spots may appear in the first week, but more often in the second, and tend to come in crops. They may not appear until the temperature is normal. In warm climates, many European skins are apt to show spots more or less like those of enteric fever, as the result of mosquito-bites and of inflammation of hair follicles or sweat-glands. Great care must be taken in discriminating between the true spot and these "pseudo-rose spots." There are many European skins which, in spite of the trying conditions of the tropics, remain free from blemishes of this sort, and in these cases the recognition of the typical spots is relatively easy.

Summary of clinical diagnosis.—Every undiagnosed fever in the tropics should be regarded as a possible case of enteric fever and closely observed clinically, at the same time that bacteriological and serological investigations are being carried out and Marris's atropine test is applied. While valuable clinical evidence may be obtained from occasional signs, such as epistaxis, pea-soup stools, abdominal distension, and hæmorrhage from the bowel, the diagnosis should rest in the great majority of cases upon the presence or absence of the five cardinal signs. Any case presenting the first, second, and third signs should be treated as enteric (whether

the diagnosis is supported by laboratory findings or not) until some other definite diagnosis is made. No case which does not show the first, together with at least two of the remaining four cardinal signs, should be definitely regarded as enteric. Five types of temperature chart have been described, any of which excludes enteric. These, however, imply that the case has had its temperature recorded from the outset, which is not often possible. In the majority of cases of active enteric fever, all five signs are present at one or other stage of the illness.

Finally, it should be remembered that, for every case of enteric fever which imitates some other disease, there are at least a score of cases of other diseases imitating enteric (malaria, trench fever, phthisis, liver

abscess, syphilis, etc.).

Paratyphoid-C.—This, as observed by Giglioli in British Guiana, although essentially a "fever" producing a temperature chart not unlike those of other paratyphoid fevers, is a septicæmia, and the intestinal tract may not be specially involved. Complications such as arthritis, abscess formation and cholecystitis are common, whilst fixation abscesses from intramuscular quinine injections may occasionally contain a pure culture of the bacillus. There appears to be a special connection between paratyphoid-C infection and malaria. The mortality of Giglioli's series of 92 cases of definitely diagnosed paratyphoid-C infections was 38 per cent. Probably a great number of abortive and mild cases passed unobserved. A few cases were reported in the Army in India during recent years.

Bacteriological diagnosis of "enteric".—(a) Hæmoculture is unquestionably the most satisfactory method of diagnosis; it should be employed, wherever the necessary facilities are available, in every case of undiagnosed pyrexia in the tropics as soon as a blood-film is found to be free from malaria parasites. A successful hæmoculture furnishes the only conclusive evidence that the patient is suffering from active enteric fever, and can hardly be said to be open to fallacy. Unfortunately, however, the usefulness of the method is limited by the short duration of bacillæmia. In many cases which are undoubtedly enteric, negative results are obtained because hæmoculture has been attempted too late. Recent experience has shown that culture from the blood-clot gives the highest percentage of positive results. Culture of material obtained by sternal puncture (medulloculture) has been shown to be useful in paratyphoid B infections, and in China it has proved to be more practical and reliable than blood culture.

(b) Culture of excreta.—Urine and stools should be plated when blood-culture has failed, and this should be repeated during convalescence to determine whether the patient is free from infection. Bacilluria occurs after the fourteenth day in about 25 per cent. In about 75 per cent. of cases, and, under modern conditions, by employing the brilliant green enrichment method, tetrathionate broth or Wilson and Blair's agar medium for concentrating the typhoid and paratyphoid bacilli, cultivation of the organisms from the fæces in all stages is now successful. Glass and Wright (1937) showed that this method gave a high percentage of results, especially in the early stages; so that during the first two weeks it is more likely to

be successful in diagnosis than the Widal reaction. Some positive findings from culture of excreta are open to fallacy. The case may be one of an enteric carrier suffering from some illness other than enteric—e.g., malaria or trench fever. The detection of carriers can only be effectually carried out in a fully-equipped laboratory; at least seven separate and consecutive bacteriological fæcal tests are necessary.

Serological diagnosis.—The Widal reaction, or the agglutination of the enteric bacilli by the serum of infected patients, is the most reliable test for

diagnosis.

When used for uninoculated subjects it gives a reliable diagnosis in the great majority of cases. However, possible fallacies are that a positive test may result from a previous attack of enteric and a negative result may be obtained in the early stages of the fever; should, however, the clinical manifestations be suggestive, the test must be repeated on several occasions. There are, it is true, exceptional cases of enteric, especially paratyphoid A, which may fail to develop agglutinins in the serum. The modern view about this test is that it must be both qualitative as well as quantitative. In inoculated persons specific agglutinins are produced which are difficult to distinguish from those caused by infection. Thus their recognition has not any diagnostic significance. In recent times differences in the agglutinins have been established. These are known as H and O. Their significance varies and they also differ in their titres, which fluctuates in relation to the progress of the disease.

The enteric bacilli—S. typhi, S. paratyphi A, B and C—are usually motile and so have flagellar (H) and somatic (O) antigens. The H antigens of these organisms differ from one another, but B and C possess a common "group" phase antigen which is also found in many other organisms of this group (Salmonella). The O antigens are also different, but there exists a considerable degree of relation between these, e.g., S. typhi and S. para B. In order to test for H agglutinins formolized suspensions of the organisms are used, whilst for O agglutinins an alcoholized suspension is substituted. In Europe suspension of S. typhi H and S. para B H (specific phase) and Salmonella H (group phase), S. typhi O and para B O are used, but in the tropics S. para A or C, H and O

are included.

Inoculation of normal persons with T.A.B. vaccine produces both H and O agglutinins, the O usually falls to a low level after the lapse of a year or so, but the H agglutinins persist for many years and are liable to be restimulated by various febrile illnesses such as influenza and malaria. This is a most important fact which is often overlooked. It therefore follows that, in inoculated subjects, the H agglutination is of little value in diagnosis, whilst in those who have been repeatedly inoculated the appearance of O agglutinins is also of doubtful value. Significant titres of agglutinins can only be assessed when the local "normal" frequency is known. Generally speaking an H titre of 1:50 or over in a patient with fever, and about the 7th–10th day of illness would certainly be diagnostic. An O titre of 1:100 or over, whether the patient is inoculated or not, would also be significant.

In doubtful cases it is necessary to repeat the test in a few days in order to observe whether the titre of agglutinins is rising or not. It was demonstrated by Dreyer and colleagues that if an estimate is made of the agglutinin content of the serum early in enteric fevers and repeated at intervals of a few days a steady rise to a maximum, followed by a slower fall, ensues. The maximum titre usually occurs between the eighteenth and twenty-first days of the illness.

From recently isolated virulent strains an additional labile body antigen can

be recognized. This is known as Vi antigen which may render the organism insensitive to O agglutinins. In acute clinical infections Vi antigens usually appear early and are extremely transient. The chief importance of this antigen is that it is found in the serum of chronic carriers of true typhoid as well as paratyphoid bacilli. They thus constitute a useful pointer to a possible carrier state, indicating that intensive bacteriological examination of fæces, urine and duodenal juice must be undertaken; they can also be used as an additional test in proving that a person is free from infection before discharge from hospital. Vi agglutinins differ from the others in that they are not stimulated by the vaccines of T.A.B. which are commonly employed and which are killed by heat and preserved with phenol. They may, however, be produced by the newer alcoholized vaccines. It has therefore become apparent that the original claims made by Felix that H, but not O agglutinins are produced as the result of passive inoculation and not as the result of infection by living organisms, now appears to be incorrect.

Atropine test.—This test, devised by Marris, depends on the fact that in health, or disease other than enteric, a hypodermic injection of atropine sulphate $(\frac{1}{3},\frac{1}{3})$ gr.) is followed by a rise in the pulse-rate amounting to at least 15 beats per minute, whereas in enteric no such rise follows. Should there be any rise at all, it will be less than 14 beats per minute, but often there is none.

The patient should lie horizontally and remain at perfect rest. He should not be tested until at least one hour after the last meal. The pulse-rate should be counted for at least ten minutes, and then gr. $\sqrt{3}$ of atropine should be injected over the triceps region. After an interval of twenty-five minutes the pulse should be counted again, minute by minute, until it is clear that any rise which may have followed the injection has begun to pass off. The period of the disease during which the test is most reliable is said to be the fifth day to the end of the second week.

Auxiliary methods of diagnosis.—The diazo-reaction in the urine is useful, but may be present in malaria. Russo's methylene-blue test is said to be more conclusive, as it is absent in malaria.

Differential diagnosis.—The abdominal pain of enteric may be mistaken for appendicitis, but the matter may easily be settled by a leucocyte count, which in the former shows a leucopenia with a relative lymphocytosis, and in the latter an active leucocytosis. Bacterium coli infections may resemble enteric. Typhus is notably difficult to distinguish in its earlier phases, though the leucocytosis in that disease may be of considerable assistance.

It must not be forgotten that enteric fever may co-exist with some other acute infection such as malaria.

Diagnosis of typhoid from paratyphoid.—There is no clinical feature to distinguish the typhoid and paratyphoid infections from one another with any certainty. Yet there are general points in which they differ. Thus, typhoid fever (Sal. typhi) is the most severe of the group, with the highest case-mortality (15 per cent. or over, as compared with 2 per cent. or less for the paratyphoid fevers). The typhoid patient looks more toxic; his temperature is, on an average, higher, with smaller morning remissions; he more frequently shows evidence of gross intestinal lesions (ulceration) e.g. diarrhæa, hæmorrhage, abdominal distension, perforation. The rash is more scanty and the individual "rose spots"

are smaller and slightly darker than in paratyphoid. There is greater loss of flesh in typhoid than in paratyphoid. Paratyphoid is characterized by a milder toxemia. There is seldom abdominal pain or distension, and constipation is the rule. Hamorrhage and perforation are rare. The rash is more profuse and may cover the entire body and limbs.

But typhoid is frequently of the very mild type, and, on the other hand, paratyphoid may be like the worst typhoid. It is therefore quite impossible to say on clinical grounds alone whether any individual case is one of typhoid or paratyphoid.

Still less is it possible to arrive at a differential diagnosis on clinical grounds between A, B, and C cases of paratyphoid, although here again, over a series of cases, distinct clinical differences can be noticed. For example, relapses in paratyphoid-A are more frequent than in any other of the enteric infections, and less frequent in paratyphoid-B. Paratyphoid-A is, on an average, of longer febrile duration than paratyphoid-B, but the latter, on the other hand, is more often followed by jaundice, thrombosis and suppurative complications.

Treatment.—There was until 1948 no generally accepted specific therapy for enteric fever; and, with the exception of chloromycetin, no drug is known to exercise an active influence over this disease. It is best to confine treatment to providing the best hygienic conditions, good nursing, and careful dieting. All that the great majority of mild paratyphoid cases require is a soap-and-water enema every other day to relieve the constipation. Milk should be the diet while the patient is febrile; thereafter custard, milk pudding, soup, fish, and meat diet. The diet should contain about 70 grm. of protein a day, with a caloric value of 2,500–3,000. Water should be given freely. Purgative medicines should be avoided. The care and cleanliness of the mouth and teeth are important.

In cases marked by great toxicity with high temperature (over 102.5° F.) and no morning remissions, tepid sponging is beneficial; in the worst cases the cold bath or ice pack may be used. The temperature of the water should be between 70° and 85° F.; a tub of canvas and mackintosh sheeting may be improvised. Food may be given as a stimulant after the bath. The rectal temperature should be taken immediately on removal from the water, and again three-quarters of an hour later.

Felix's antiserum treatment.—Working on his observations on the virulence of smooth strains of S. typhi towards the "O" antibody and the Vi antigen which is definitely associated with virulence, Felix (1935) produced an efficient antiserum from horses by injecting the Vi antibody. The therapeutic effects of this scrum have been tested in a number of cases in Palestine and in Dublin. The results so far obtained are encouraging, for they indicate a favourable action on the toxemic manifestations of the disease and the pyrexia. The dose is 25 ml. of serum on three successive days. In very severe cases this dose may be doubled. McSweeney reported the recovery of a dangerous relapse treated in this manner, as well as of a child of four years with typhoid meningitis in which the organism had been recovered from the cerebro-spinal fluid.

Chloromycetin (chloramphenicol).—In vitro this antibiotic inactivates S: typhi in 0.25 mgm. per ml. Ten cases treated by Woodward and colleagues in Malaya (1948) with initial oral dosage of 50 mgm. per kg. body weight, thereafter 0.25 mgm. every two hours till the temperature was

normal, did well and the mean duration of fever was 3.5 days after treatment. Two patients, however, subsequently relapsed with bacterizemia. These results have in the main been confirmed by Murgatroyd and others (1949), but it has no apparent effect on the typhoid bacilli or on typhoid carriers. It is agreed that the treatment should extend over 14 days at 50–100 mgm. per kg. daily.

Smadel, who has had an extensive experience of this treatment, finds that there is little, if any, clinical improvement in the first 36 hours and patients usually become afebrile about the fourth day. The bacteriæmia ceases several days before the fever and toxæmia subsides. In his latest reports he emphasizes that cortisone given together with chloramphenicol controls the fever more completely. Cases become afebrile 15 hours after the combined therapy has been initiated, when a total of 200 mgm. cortisone and 4.5 grm. chloramphenicol had been given: even then, it was found that an intestinal hæmorrhage continued for some days longer. The larger the doses of cortisone, the shorter the afebrile period, for it was shown in eight cases when given 200 mgm. cortisone on the first and 100 mgm. on two succeeding days, together with chloramphenicol, that pyrexia was limited to fifteen hours only.

The largest series of treated cases come from Chile and the Philippines. In the former Kraljevic, Perroni and others gave capsules of 250 mgm. chloramphenicol and, after an initial loading dose, daily maintenance varied from 1–6 grm. in divided doses every 2–3 hours. Nevertheless melæna occurred in eight, perforation in five, and there were six deaths.

Valdivieso, also in Chile, rates chloramphenicol as specific, but if administration is stopped too early relapses occur. The best scheme is in 50 mgm. doses one every four hours and kept up for ten days after the treatment has fallen to normal. Lantin and colleagues in the Philippines give a loading dose 1–2.5 grm. followed by 0.25 grm. every 2–4 hours during the febrile period and at lengthened intervals of one week after the temperature has settled. In the most seriously ill and toxic cases chloramphenicol seems to hasten death and then may be contra-indicated.

Recent papers suggest a combination of aureomycin and chloramphenicol may be better.

For the bacilluria associated with enteric, urotropine (hexamine) in doses of gr. 10 three times a day usually acts, though the sulphonamides—

sulphapyridine especially—have proved more efficacious.

In hæmorrhage, all fluids should be stopped for at least 48 hours, and sufficient morphia injected to keep the patient at rest. Though a very large amount of blood may be lost without causing a fatal result, yet, when feeding is recommenced, it should be proceeded with very carefully. As a general rule, one large hæmorrhage is less serious than a number of smaller ones. When bleeding has ceased, a subcutaneous infusion with saline up to 1½ pints may be permitted, and this may be repeated later should no further hæmorrhage occur. Blood transfusion has been employed with advantage and appears to arrest the hæmorrhage. It is advisable, should hæmorrhage be suspected, to give 30 gr. of calcium lactate three times daily; some make a practice of doing so from the sixteenth to the twentieth day of a typhoid fever, and from the fourteenth

to the eighteenth day of a paratyphoid. In thrombosis, sodium citrate is indicated.

Prophylaxis.—Anti-enteric inoculation has been conspicuously successful, as shown by the statistics of the American Army, and of the British Army in India. During the 1914–18 war the vaccine was modified by the introduction of S. paratyphi-A and -B, and the statistics furnish conclusive evidence of the efficacy of this measure of prevention, not only in lessening the incidence, but also in modifying the disease or diseases. Therefore, everybody proceeding from a country such as England to the tropics or subtropics should be inoculated with two doses of triple vaccine (T.A.B.), and should be re-inoculated every year subsequently with one "booster" dose, 1 ml., so long as he remains in a country where enteric is prevalent.

The typhoid vaccine, as originally introduced, caused a considerable reaction, but by better methods of preparation and dosage in recent years the reaction has been mitigated. The official vaccine contains 1,000 millions of typhoid bacilli, 750 millions of paratyphoid-A, and an equal number of paratyphoid-B, to each c.c. Two doses of 0.5 c.c. and 1 c.c. are given at an interval of ten days. The reaction in the majority of instances is slight. Occasionally, however, cases of persistent pyrexia with severe local symptoms, malaise, and headache are met. In countries where paratyphoid-C is prevalent a tetravalent vaccine should be employed.

Preparation of the vaccine.—The organisms are grown upon trypsin-agar, washed off in saline and killed by heat. The vaccine is then standardized by combining the various bacterial suspensions in their appropriate proportions. The final emulsion is preserved by the addition of 0.4 per cent. lysol.

Statistics.—During the South African War, when prophylactic inoculation was incompletely practised, there were 60,000 cases of enteric, with 8,227 deaths. With millions of men under arms during the first two years of the 1914–18 war, only some 4,000 cases of enteric were reported from France, with a case-mortality of less than 2 per cent. In the Navy, Bassett-Smith's statistics record an incidence of only 144 cases of enteric during the year 1917, of which 8 occurred in inoculated and 136 in uninoculated individuals.

The American Army shows much the same figures; for two years, 1917-19, among an average strength of over two million men, there were only 213 deaths from enteric, and it is calculated that, had typhoid prevailed in the same proportion as in the uninoculated troops in the Spanish-American War, the death-roll from this cause would have been over 60,000.

In the Royal Air Force a dissolved T.A.B. vaccine is used, the solvent being sodium lauryl sulphate. This vaccine is prepared by Glaxo Laboratories. When injected it gives rise to reactions considerably milder than did that formerly employed, though it appears to produce an equal quantity of bactericidal bodies in the blood of inoculated persons. No definite correlation has been found between the H and O agglutinin titre and the bactericidal potency of the human sera tested.

The problem of enteric infections among natives employed in the Rand Gold Mines has given rise to a considerable degree of anxiety. In seven years (1930-37) the number of cases was 6,611, and the "carrier problem" among these people is very serious. In December, 1936, inoculation with endotoxoid vaccine was initiated, with a great diminution in the number of cases of "enteric" notified.

The prophylactic inoculation against typhoid and paratyphoid fevers has been recommended by the Transvaal Mines Medical Officers' Association.

Vi antigen.—Felix has shown that in typhoid and paratyphoid formalin (commonly used for killing cultures) has a definite deleterious action on "O" antigen which is concerned with typhoid immunity, whereas heating to 60° C, or higher, leaves this antigen intact. Another antigen of typhoid—the Vi antigen—which Felix maintains is connected with typhoid immunity, is destroyed by heating to 60° C, or by formalin, but can be preserved by killing the bacteria with 75 per cent. alcohol.

Vi alcohol-killed vaccine is under trial. The vaccine retains its power after storage in the cold for at least nine months. Felix, Rainsford and Stokes compared this Vi vaccine (T.A.B.) with ordinary heat-killed T.A.B. and T.A.B.C. vaccine from various sources. Two marked differences were found between groups of subjects inoculated with the two types: alcohol-killed and preserved vaccines stimulated demonstrable Vi antibodies in a relatively high proportion, whereas the Vi antibody response to ordinary vaccines is negligible. No significant difference in O antibody response was observed. Reactions produced by alcoholized vaccines were milder than by the ordinary method.

Felix's Vi Vaccine contains:

1,000 million So 500 ,, A Dosage.		<i>hi</i> . C. per.	ml.		1st dose.	2nd dose.
Adult males					0-25 ml.	0.5 ml.
, females	3				0-2 ,,	0-4 ,,
Children						
16 -1 8 .					0-2 ,,	0-4 ,,
13-15 .					0-1 ,,	0.2 ,,
9-12 .					0.05 ,,	0.1 ,,
under 8 .					0-05 ,,	0.05 ,,

Interval between injections: three weeks; revaccination advisable one year after primary immunization. The injections should be made as late as possible in the day.

Measures to avoid infection.—The most effective method for avoiding enteric infection is the water-carriage system of sewage-disposal. This, however, is not general in the tropics, so that other methods must be considered. They are: (a) detection of enteric carriers and their control, especially in relation to the selection, distribution and cooking of food; (b) protection of water supplies; (c) extermination of flies, and preventing them from access to excreta and refuse on the one hand, and to food for human consumption on the other.

ENTERIO-LIKE FEVERS

Septicæmia due to Bacterium alkaligenes and other organisms.—During recent years a series of mild pyrexias, of either remittent or intermittent type, has been proved by Hirst and others to be due to infection with Bact. alkaligenes (Table VII, p. 473). It is a common inhabitant of the intestinal canal, where it is not definitely known to exert any pathogenic action. The fever it gives rise to in the blood-stream may last from two to fifteen days. There is an evening rise with marked morning remission. The symptoms

resemble those of a mild enteric, the pulse is slow in relation to the temperature, and the tongue is slightly furred. In some cases the patient's serum agglutinates

the homologous organism in a dilution of 1 in 50.

In outbreaks of food-poisoning or "ptomaine poisoning," which occur from time to time, bacilli of the Salmonella group, Sal. enteritilis, S. suipestifer, have been isolated from the bloodstream. The fevers they produce have many features in common with enteric. They differ in the suddenness of the onset, with rigors, the accentuation of the gastro-intestinal symptoms, the short duration and rapid termination of the fever. S. suipestifer resembles S. paratyphi-B in its biochemical, but may be differentiated by its serological reactions.

Bacterium (Eschereria) coli infections.—Infection of the bladder and urinary tract with Bact. coli is frequently met in both sexes in the tropics. Should the organism enter the bloodstream it may give rise to a prolonged intermittent pyrexia resembling enteric. Bact. coli septicæmia and pyæmia may be a terminal infection in debilitated persons, especially as a sequel of bacillary dysentery; in these cases the organisms gain entrance to the bloodstream through the intestinal lesions, and, becoming arrested in the glomeruli, give rise to multiple and minute abscesses in the cortex of the kidneys, from which they escape intermittently and appear in the urine (Fig. 51). The condition, which was first described in Egypt by Enright and the Editor, has now been found fairly commonly as a sequel of bacillary dysentery in the Middle East. The general condition of the patient, the stupor and the intoxication, may resemble those of enteric, but the onset is generally sudden, with headache, and acute pain referred to both kidney regions. Usually vesical irritation is absent. The tongue is thickly furred; rigors are numerous and accompanied by profuse sweats. The organism may be recovered in pure culture from the bloodstream during the rigors, as well as from the urine by ureteric catheterization. The acute attacks are apt to be confused with those of malaria. This form of Bact. coli infection is amenable to sulphonamide (sulphapyridine and sulphadiazine) treatment and streptomycin.

Pyelitis.—It was formerly considered that the anatomical relationship of the renal pelvis to the colon determined the frequency of infection, especially in women, but Leishman (1939) found that looseness of the bowels was the most frequent determining factor, suggesting an ascending infection. The symptoms may commence with a rigor and a dull aching pain in the loins which is increased on pressure. Micturition may be frequent, and sometimes a large and tender kidney may be palpated. The results of the inflammation are soon seen in the urine, which contains albumin, pus cells, and sometimes even blood. Bact. coli is present in large numbers, especially in the first specimen of urine passed during the day. Differentiation from malaria, which it may closely resemble, may be necessary. Cystitis with pyrexia and acid urine may also be due to Bact. coli and is very apt to occur as a sequel to any debilitating tropical fever, especially enteric infections. It is always necessary to consider this possibility. Bact. coli infections of the urinary tract are quite commonly engrafted upon some other more serious infection, such as tuberculosis, and may mask the original picture of this disease. The possibility of ascending infection of the ureters from a long-standing prostatitis or urethritis in the male must not be ignored. In women this may be a sequel of miscarriage or parturition.

Treatment.—The treatment of Bact. coli infections of the urinary tract, which is so important in tropical practice, has been placed on a much surer and more satisfactory footing by modern discoveries in therapeutics. It was found that the excretion of ketone bodies in the urine destroyed the greater number of the Bact. coli organisms, and this led to the application of mandelic acid,

which produces similar changes in the urine. Mandelic acid is related to β -hydroxybutyric acid and produces a high degree of acidity—pH5—in the urine, together with acetone. A methyl-red indicator is employed to estimate the hydrogen-ion concentration.

The original mandelic acid method has now been superseded by the use of more modern preparations, such as ammonium mandelate, mandelix and

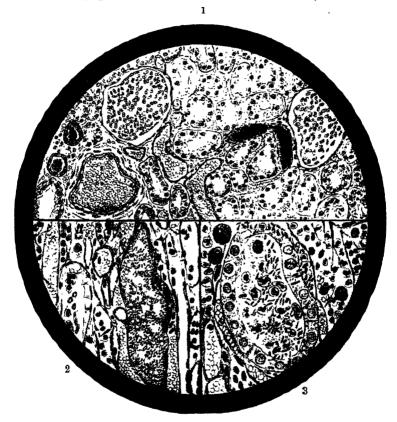


Fig. 51.—Sections of kidney in Bact. coli septicæmia.

Aggregation of organisms in intertubular capillaries;
 large collection of organisms in a medullary vein;
 passage of bacilli through tubular epithelium of duct of Bellini into lumen.

mandecol, in which ammonium chloride is combined with mandelic acid. These preparations are given as 1-2 drachm doses three times daily directly after meals until the urine has become sufficiently acid, the fluid intake being restricted to 40 oz. daily, and are very often successful in cases of pure *Bact. coli* pyelitis.

Sulphonamides are especially useful in *Bact. coli* cystitis and trigonitis. Sulphapyridine and sulphadiazine in doses up to 3 grm. daily for 10–14 days may be reinforced, if necessary, by after-treatment with mandelic acid preparations. A better preparation is "Steramine," which is sulphacetamide¹ (N₁ acetyl derivative of sulphanilamide). It possesses a low toxicity with high antibacterial activity.

Albucid is the alternative trade name

In most acute cases the dose is 2 grm. initially, followed by 1 grm. four-hourly for two days, then I grm. six-hourly for two days and finally I grm. eight-hourly for a further two days. In obstinate cases treatment lasting 10-14 days may be necessary. Intravenous injections of 5 ml, of a 30 per cent, solution may be given at the commencement of the course. No attention need be given to the pH value of the urine. Proportionately smaller doses are necessary for children Fergusson, Reinold and Wriglev (1948) have found that a new sulphonamide— NU-445 (Roche)—dimethylsulphanilamido-isoxazole—gives the best results in urinary infections. The initial dose is 3 grm. followed by 2 grm. at eight-hourly intervals until 31 grm. has been given over a period of five days. The drug has a greater bacteriostatic effect in slightly alkaline urine. The toxic manifestations of these drugs, which include methæmoglobinæmia, are not common. In some patients they may produce headaches, or even drug fever and abdominal pain It is necessary to estimate the leucocyte count at regular intervals, as leucopenia. or even agranulocytosis, may supervene. Streptomycin when injected in full doses gives good results in sterilizing the urine. Recent reports indicate that aureomycin has the same action.

It must be emphasized that, in employing these therapeutic measures, the condition of the kidneys and ureters should first be ascertained by means of excretion urography (uroselectan). Sometimes a calculus may be discovered in the renal pelvis or in the ureters, which may be the seat of the Bact. coli

infection, necessitating surgical intervention.

Subsection E.—DISEASES CAUSED BY VIRUSES

CHAPTER XVII

YELLOW FEVER

Synonyms.—Typhus icteroides; Fièvre jaune; Fiebre amarilla (Spanish); Gelbfieber. "Amaryl"—International nomenclature.

Definition.—An acute, specific febrile infection, due to a filterable virus, occurring epidemically, or endemically within a limited geographical area. It is primarily an infection of monkeys in which it is largely asymptomatic. Though subject to great variation and occurring sometimes in a mild form, both in Africans and in Europeans, its typical clinical manifestations may be said to be a sthenic initial stage, rapidly followed by an adynamic condition. Jaundice and albuminuria commonly occur. One attack confers immunity for life. The virus is transmitted principally by female aëdine mosquitoes, which remain infective during their lifetime.

Geographical distribution.—This is considerably wider than was formerly supposed, though in the 18th and 19th centuries outbreaks occurred in areas where they are no longer seen. For a great deal of our knowledge we are indebted to the labours of the International Health Division of the Rockefeller Foundation which, by means of the mouseprotection test (see p. 836), has shown that it can be determined whether yellow fever has been present in a district during the lifetime of the present inhabitants and, from the ages of those with positive protection, when the last epidemic occurred. At present yellow fever is mainly confined to South and Central America, and in Africa south of the Sahara from the Atlantic Coast to the Red Sea and Indian Ocean (Map IV). In comparatively recent times it is known to have been widespread in the West Indies, Mexico and in the United States, as far north as Philadelphia (1793) and Memphis (Mich.) (1878), and as far south as New Orleans and Galveston (1905). During the last century it was imported from time to time by ships to the Canary Isles, Spain, Portugal and to the small islands of Ascension and St. Helena in the South Atlantic, in all of which limited outbreaks took place. In 1865 a few cases occurred in Swansea, South The disease has never invaded Asia or Australia. It is still by no means certain whether yellow fever originated in West Africa and was conveyed by ships to the West Indies and South America, or whether the disease was enzoötic in America before the coming of man.

In South America yellow fever was endemic in Brazil, Bolivia, Colombia, Peru, Venezuela and Guatemala, and there is some evidence that it still exists in British and Dutch Guiana. In their campaign against yellow fever the Rockefeller Foundation concentrated on eradicating the "seedbeds of infection" on the South American continent in the belief that they were few. The clearing of Rio, Santos and Nichtheroy was followed by apparent disappearance of yellow fever from the whole of Southern Brazil. After a campaign in Guayaquil and another in Peru in 1920, no further cases were recorded on the Pacific Coast. Similar results were

obtained in Colombia, Mexico and Central America. Yellow fever reappeared in Panama in 1948–1949 after an absence of forty years when four cases of the jungle variety were diagnosed (Herrera).

In 1928-1929 yellow fever reappeared in Rio de Janeiro. Soon locally infected cases occurred in the Brazilian States of São Paulo, Minas Geraes,



MAP IV
Distribution of Yellow Fever in Africa

Rio, Bahia, Sergipe, Pernambuco and Para. In 1932, by the introduction of the viscerotome, an instrument for obtaining liver tissue for examination, it was possible to prove the existence of "jungle yellow fever" (in the absence of Aëdes agypti) in Espirito Santo. This is now regarded as the original and more permanent form of yellow fever. In West Africa yellow fever has long been known from Senegal to the Congo, while the long story of British endeavour in the development of this country, especially Sierra Leone and the Gold Coast, is one of struggle against yellow fever. (In 1826, out of the garrison of 585 soldiers, 115 were dead

within two months, while of the first detachment of troops which occupied Cape Coast Castle in 1823 only one man was alive a year later. In 1878 an epidemic involved the whole of Senegal, affecting 1.474 Europeans.)

In the epidemic in Accra in 1987 the native population and Syrians were alone affected. Small outbreaks took place on the Congo at Matadi and Boma in 1927 and 1928, at Bathurst on the Gambia in 1935, and there were numerous other cases on the Gold Coast and in Nigeria in 1937 and 1938. The most extensive epidemic of yellow fever recorded in Africa broke out in the Nuba Mountains, Southern Sudan, in May, 1940, and there were 17,000 cases with a mortality-rate of 10 per cent. Previous to this, one single case of yellow fever had been recognized at Malakal in 1934. The epidemic subsided in November and was followed by a rise in the proportion of immunes in the population.

An epidemic confined to non-Europeans occurred in Nigeria in 1946 and in 1951 in the northern Province.

Recent Information.—The fact that severe and fatal cases have not been seen, or recognized, does not warrant the assumption that an area is free from this infection.

Congo area, in 1940 yellow fever was reported at Yatolema near Stanleyville, in Northern Rhodesia in 1943 at Balovale, in Southern Rhodesia on the Zambesi River and in North West corner near the Angola border.

Anglo-Egyptian Sudan.—Additional evidence from the Fung area has shown that yellow fever has recently occurred as far East as the Abyssinian border. In the equatorial province, East of the White Nile, yellow fever is widely distributed. A fatal case in a European was reported in Torit in 1942 and also one in Kapoeta. Immune sera have been found in the Imatong tribe in the Imatong Mountains.

In Southern Abyssinia one protective serum has been obtained.

Eritrea.—The evidence is that yellow fever has recently occurred in coastal areas and in the western plains, near the Red Sea coast, and also in Somalia.

Kenya.—A fatal case occurred in Kitale in 1942 and a second in 1943. Immune sera have been found in the adjoining Langata forest.

Zanzibar and Tanganyika have been found free from recent infection.

It has now been shown, as the result of immunity surveys, that yellow fever extends in a region from St. Louis on the coast of Senegal, just north of Cape Verde, eastward at latitude 15° N. along the southern borders of the Sahara through El Fasher to Dilling in the Southern Sudan. Thence the line bends southwards at Rashad in the Nuba Mountains, crossing the White Nile south of Jebelein, passes through Dar Fung, the area between the White and Blue Niles, up to and possibly beyond the Sudan-Abyssinian border. An extension eastward has been established to the N.W. boundary of Eritrea and the Red Sea coast, thence S. to the border of Somalia, at 36° meridian of longitude, south of Lake Rudolf. The eastern border runs through Western Uganda to the west of Lakes Victoria and Tanganyika, and thence diagonally at 10° S. parallel, across the Belgian Congo to the mouth of that river. In the west the line follows the Atlantic coast from Senegal to Santo Antonio in the extreme north

of Angola: a total area comprising approximately four million square miles. The islands in the Gulf of Guinea are included as well as the Balovale district of Northern Rhodesia and part of Bechuanaland. (Map IV.)

In the Western hemisphere the endemic area is bounded by a line running from Turbo in North Colombia directly south to the northern boundary of Ecuador and thence along the eastern slopes of the Andes, below an elevation of 6,000 feet, to the northern boundary of Argentina; thence east along the twenty-second parallel of latitude to the west border of Brazil, thence in a north-east direction to the junction of the states of Maranhoa and Para on the Atlantic Coast of Brazil, and thence along the Atlantic and Caribbean coasts of South America to Turbo. In addition the Isthmus of Panama, from the canal zone to the border of Panama and Colombia, and the Ilheos and Itabuna districts in the state of Bahia in Brazil are regarded as endemic areas. (Map V.)

Finally, it is obvious that the geographical distribution of yellow fever does not correspond with that of A. ægypti, as the Orient, with its susceptible population and abundance of suitable mosquitoes, has so far remained

free.

Epidemiology.—In former times it was generally considered that yellow fever was mainly confined to seaports and that it seldom spread far inland, but this is now known not to be the case. A study of epidemics shows that the virus of yellow fever can be readily transported from one place to another and that for its development in the mosquito it requires, usually, a mean atmospheric temperature of 75° F. (24–25° C.), and that endemic centres have never extended beyond 40° N. Lat. and 35° S. where the isotherm is not below 68° F. (20° C.). A high wet-bulb temperature favours yellow fever, so that it is most likely to arise and spread during the rainy season. It may, however, be found in mountainous regions up to 4,000 ft. In spreading inland it appears to follow lines of communication.

Conceptions on the epidemiology of yellow fever have had to be considerably revised since the discovery of the jungle form. Some authorities recognize three divisions—urban, rural and jungle—the last of which is thought to be the most primitive. Soper, on the other hand, favours

the following classification:

(1) The urban and rural types are a domestic and purely human disease with a simple cycle of infection depending upon man and the insect vector, Aëdes ægypti, but these forms cannot spread in the absence of A. ægypti mosquitoes in sufficient numbers.

(2) Jungle yellow fever, involving man and animals, in the absence of Aēdes œgypti, indicates that neither this insect nor man himself is an essential element in the insect-vertebrate cycle of infection which main-

tains the reservoir of the virus in the jungle.

Jungle Yellow Fever.—It is now known that this form of yellow fever is conveyed by the bites of certain jungle mosquitoes (in Bolivia, Colombia and Brazil by Aëdes leucocelænus, Hæmagogus spegazzimii falco and possibly also Sabethoides mosquitoes). There is now little doubt that jungle yellow fever exists also in Africa, where isolated cases have been found in the bush. The most important focus about which we have definite information was discovered by Mahaffy and his colleagues in 1941 in North Uganda, on the

Semliki, west of Ruwenzori and on the eastern reaches of the Ituri river (Bwamba country). The northern half of this country is heavily forested, uninhabited except or pigmies. There the virus of yellow fever was isolated from humans as well as from a wild-caught mosquito—Aèdes simpsoni—which appears to be the vector in this area.



MAP V
Distribution of Yellow Fever in South America

Bwamba lies in the extreme west of Uganda bordering on the Belgian Congo and is a lowland forest area bounded by the rivers Semliki and Lamia as well as by the Ruwenzori mountains. The population is sparse on the mountain slopes and grassy plains, but more dense in the cultivated strips in the foothills. The fertile area is crossed by mountain streams. Larvæ of some tree-hole breeding mosquitoes occur in rot holes in soft-wooded figs and in pools enclosed in their buttress roots, but not in water held in fallen leaf tracts of the umbrella tree (Musanga smithii). Outside, the forest fig and Cassia plantations are the haunts of tree-hole breeders. The climate is warm and fairly equable. The highest temperature recorded is 98° F., but it rarely falls below 15° C. (59° F.). Humidity is high and approaches saturation during the cooler parts of the day.

The annual rainfall is 50-60 inches, occurring in two rainy seasons, vernal and

autumnal equinoxes.

The evolution of epidemics of yellow fever.—In experimental infection of humans the shortest incubation period recorded is about two days, but under natural conditions, it is from one to six and a half days. A period of at least fourteen days may elapse between the arrival of a yellow-fever-stricken patient in a hitherto uninfected district and the first case of the epidemic to which he may give rise. This would indicate that the period between the introduction of the virus into the body and the development of fever is usually some three to five days, yet a period of at least twelve days must elapse before that virus, removed from the human body, can be transmitted by mosquitoes to another man. This is known as the extrinsic period and represents the time taken for the virus to multiply inside the mosquito, though experiments with these insects, when fed on monkeys, show that this may be reduced to eight or nine days at high temperatures; at low temperature the mosquitoes may never become infective.

Conditions favouring endemicity.—For yellow fever to continue in an urban community three factors are necessary: (1) the virus, (2) the vector, and (3) susceptible human beings living under conditions in which both virus and man are easily accessible to the mosquito. A break in this chain suffices to eliminate the disease. In the urban, and more especially in the rural type, yellow fever cannot continue to exist in a community, unless Aëdes ægypti mosquitoes are present in sufficient numbers. But in a population, which has become to a great extent immune to yellow fever, it is obvious that a greater number of infected mosquitoes are necessary to maintain the virus. Thus, from time to time the disease has disappeared from towns in South America in which no sanitary work had been done to eliminate the mosquito; the explanation being that there was a lack of susceptible persons to continue the existence of the virus in man.

Possibility of animal reservoirs of the virus.—The maintenance of the virus in endemic jungle yellow fever has been difficult to explain. It is possible that it might be carried on solely by the mosquito-man cycle through the combined presence of infected mosquitoes and frequent human cases. Thus, if cases were occurring continuously in man in any particular area, it should be possible to obtain the virus from the blood of these patients for, even if the vast majority had mild, or even subclinical symptoms, a few typical cases should be encountered from time to time. The second possibility is the existence of animal reservoirs. In 1914 Balfour drew attention to the great mortality amongst red howler

monkeys (Alouatta seniculus) which preceded outbreaks of yellow fever in Trinidad and Venezuela. Amongst the natives the belief was strongly held that this presaged a human epidemic. In 1935 monkeys with immune bodies to yellow fever were discovered both in South America and in Africa. Then Soper (1938), in an outbreak in the States of Minas Geraes and Rio de Janeiro, found increased mortality amongst these monkeys and, by protection tests, that they constituted an important factor in the spread of jungle yellow fever in Brazil. As the result of more recent work in South America it has been shown that inoculation of the virus into certain wild animals produces no appreciable illness, though it is still present in their blood for some days. Such animals are monkeys, marmosets, opossums of all species, especially Didelphis marsupialis, anteaters, sloths, armadillos, the agouti, paca, capybara and some mice. Their movements are not restricted, and so the virus can spread over a wide area; transmission is then probably effected by jungle mosquitoes.

Mahaffy regards jungle fever as primarily a disease of primates in the forest and to spread by Aēdes africanus but, the arboreal monkeys raid the plantations of the neighbouring Africans for food and, in doing so, they come into contact with Aēdes simpsoni which may become infected from them and in this manner spread the disease to man. This mosquito too may also enter the forest for a blood meal. In this instance Aēdes ægypti

though present, apparently plays no part in the cycle.

In Central Africa there is some suggestive evidence. Pruner's hedgehog (Atelerix albiventris) has been found very susceptible to yellow fever, and the presence of immune bodies in the blood of a monkey, Colobus badius waldroni, was verified by Findlay on the Gold Coast in 1935. He, moreover, showed that the sera of about 25 per cent. of the monkeys in Central Africa are protective.

It seems, therefore, that in rural and in jungle areas yellow fever may persist in the absence of susceptible humans. It is also a curious fact that normal cows' serum protects in certain instances. These findings seem to show that there are other methods of spread than by the mosquitoman cycle. Animals which may be concerned with the transmission of yellow fever may be classified as follows:—

- (1) Animals which on inoculation develop symptoms and die with lesions.
- (2) Vertebrates which allow multiplication of the virus in the blood and develop immune bodies.
- (3) Vertebrates which have been shown to harbour virucidal bodies in the blood under natural conditions.

The virus has been isolated from the blood of wild marmosets—Callithrix penicillata and Lentocebus chrysomelas at Ilhéus, Bahia, Brazil; and cyclic passage obtained in C. aurita and Cebus monkeys—C. versutus in combination with Aëdes ægypti and Hæmagogus equinus; a Colombian strain has been maintained with Saimiri monkeys and H. spegazzinii falco as vector.

More recently typical yellow fever lesions have been found in the Douroucouli— Aotus trivirgatus—and the virus transmitted to Saimiri (squirrel) monkeys. This is an important epidemiological fact as the former is the only monkey found in

certain areas of Colombia.

In that country too Oedipomidas edipus is the common marmoset, and the virus is transmitted from it to Aotus and Saimiri by the bites of Hæmogogus.

In Bwamba, Uganda, the general incidence of immunity of monkeys is 61 per cent. The lowland Colobus monkey (Colobus polykomos uellensis) is the main species involved in monkey to monkey yellow fever cycle, but the red-tail (Cercopitheus nictitans mpangæ) plays an important part in bringing the virus into contact with man.

According to the list given by Corson (1945) the following vertebrates are to

some degree susceptible to the yellow fever virus .:-

Africa and Asia.—Pan satyrus—Chimpanzee. Macaca sylvana, Barbary ape. Cercopithecus æthiops centralis, African grivet monkey. C. tantalus, Tantalus monkey. C. diana diana, Diana monkey. C. patas, Patas monkey. C. ascanius schmidti, Schmidt's white-nosed monkey. Colobus polykomos, King Colobus monkey. C. badius, Bay Colobus monkey. C. b. waldroni, Waldron's Colobus. Papio cynocephalus, Yellow baboon. Macaca mulatta, Rhesus monkey. M. irus, Crab-eating macaque. Galago senegalensis, "Bush baby." Erinaceus europæus, Hedgehog. Atelerix albiventris, Pruner's hedgehog.

South America.—Cebus fatuellus, Brown capuchin. C. apella, Weeper capuchin. C. xanthosternus, Small-headed capuchin. Callicebus ornatus, "Titi" monkey. Ateles paniscus, Red-faced spider monkey. Alouatta seniculus, Red howling monkey. Saimiri sciurea, Squirrel monkey. Actus trivirgatus, "Douroucouli." S. orstedii (Panama). Didelphis marsupialis, Common opossum. D. nuditicaudatus, Rat-tailed opossum. Metachirops columbianus, Brown-masked opos-

sum. Caluromys laniger, Woolly opossum.

Dog, fox, ox, sheep. goat, pig, camel and horse in Africa and South America; also:—

Thryonomys swinderianus, Great cane rat in Africa. The following birds: Bulbulculus ibis ibis, African cattle egret. Tyto alba affinis, Barn owl. Halcyon senegalensis, Senegal kingfisher. Neopelicanus rufescens, Pelican. Anastomus lamilligerus, African openbill. Strutho camelus, Ostrich, and various Cathartida, vultures in South America.

The full significance of virucidal bodies in sheep, cattle and birds requires further study.

All susceptible animals are characterized by a similarity of behaviour following virus inoculation. There is a preliminary clearance of virus from the blood-stream and after a few days it again reappears. Coincident with this later phase antibodies appear and gradually increase to a maximum extending to several months. There appears then to be no virus reservoir amongst non-human vertebrates. The demonstration of the susceptibility of an animal in the laboratory tells little or nothing about its actual part in the natural cycle of the virus. All primates are susceptible to yellow fever, although there is a wide variation in the severity of the yellow fever so produced. Although certain rodents are susceptible, they play no part in the forest cycle of yellow fever.

Immunity rate.—In areas outside the present known endemic zones of yellow fever, with few exceptions, no immunity against yellow fever exists. Thus, Sawyer and his colleagues showed that of 876 human sera from Asia and Australia only 2 gave any protection, whilst amongst 481 sera from Italy, Portugal, Canada and Northern United States of America, even from some of the localities where yellow fever was formerly present, one only was protective. Sera were also tested from the West Indies, Barbados, Jamaica, St. Lucia, Trinidad, Cuba and Porto Rico. The sera of 821 people under twenty years of age were all negative, but

above that age 8.42 per cent. gave positive protection tests. These results agree with the fact that yellow fever existed in all these regions until comparatively recent times. In Mexico, however, a higher percentage was obtained. From five to nine years, 0.9 per cent. were positive, from ten to fourteen years, 8.55 per cent., from fifteen to nineteen years, 28.81 per cent., but from twenty years and over, 42.72 per cent.

The results from the Sudan are of special interest as showing that outbreaks of yellow fever can to some extent be predicted. Villages in the Nuba Mountains, which had previously been shown to have a high percentage of immune bodies, were not attacked in the 1940 yellow fever epidemic, and in many 70 to 80 per cent. of positives were obtained, as also in the Fung area to the east of the White Nile.

Investigation of an area, immediately after the subsidence of an epidemic, by means of the mouse protection test, reveals that the number of persons who give positive protection is much greater than the actual number of cases clinically diagnosed as yellow fever.

In Central African forest the general immunity rate amongst the monkeys is very high. Over 40 per cent. are protected. Immune monkeys are found in all parts of Uganda with the exception of Ruwenzori Mountain forest. The highest rate is found in Bwamba county, Toro district and part of Masaka and Mengo districts.

The exclusively arboreal and mainly arboreal species show no significant difference in the incidence of immunity but on the whole terrestrial monkeys show a definitely lower immunity rate.

The role of monkeys in yellow fever epidemiology suggests that there may be a diurnal arboreal vector of the disease in addition to the well-known nocturnal Aëdes africanus, as in certain areas it does not seem possible for continuous monkey-to-monkey transmission to be maintained (Haddow, Dick, Lumsden and Smithburn, 1951).

Ætiology.—A great many attempts have been made in the past to discover the causal agent or virus of yellow fever and many organisms have been described. The most ill-omened was undoubtedly the Leptospira icteroides of Noguchi, which eventually proved to be identical with L. icterohæmorrhagiæ of Weil's disease. The true nature of the virus was adumbrated by Reed, Carroll, and Agramonte who, in 1901, showed that it was filterable and ultramicroscopic. This was the first occasion in which it was proved that a filterable organism might be the cause of human disease. In 1929, Stokes, Bauer and Hudson clearly proved that the agent is ultramicroscopic and passes through Berkefeld filters V. and W. In 1933 Findlay and Broom, by employing Elford's system of ultra-filtration, were able to measure the particles of the virus. Findlay and Broom estimate the size of the particles as $18-27 \text{ m}\mu$. Sellards and Hindle showed that the yellow fever virus can maintain its vitality when frozen. When transported from Dakar to London the disease was reproduced in macaque monkeys by subcutaneous and intraperitoneal inoculation. When dried in the frozen state the virus retains its vitality as long as seven and a half years.

An important advance was made by Theiler (1930) who showed that white mice can be infected with yellow-fever virus by intracerebral inoculation; the mice develop a fatal meningo-encephalitis. After a certain number of passages in mouse brains, it becomes established as a neurotropic virus, which no longer reproduces yellow fever of the usual type when monkeys are injected subcutaneously with the brain tissues of infected mice. Infection of rhesus monkeys can be produced by subcutaneous or intraperitoneal injection of infected blood or tissues or by smearing vellow fever blood on the unbroken skin: the virus may also be absorbed by the mucous membrane of the alimentary tract. In these animals the clinical and pathological picture of human yellow fever is reproduced and the virus is known as the viscerotropic strain. Rhesus monkeys artificially infected with this virus usually die from four to seven days after inoculation, before they have had time to develop immune bodies. The infective blood of monkeys may contain virus in dilutions as high as one in fifty million; the virus may penetrate cell-free and protein-free fluids, such as the aqueous humour of the eye.

The virus is so virulent that infection of monkeys may occur from the bite of a single infected Aides ægypti. The species of monkey susceptible to the pantropic or viscerotropic strains are the rhesus monkey (Macaca mulatta), the crab-eating macaque (M. irus), the brown macaque (M. fuscata) and also, to a lesser degree, M. sinicus. The Barbary ape from North Africa (M. sylvana) is also susceptible. Amongst New World monkeys, marmosets usually die, while some species of capuchin monkey recover after a febrile attack. Guinea-pigs are completely refractory, so that inoculation of these animals with blood from a suspected case serves, negatively, as a means of differentiation from Leptospira ictero-hæmorrhagia. Guinea-pigs, however, develop immune bodies after inoculation. European hedgehogs, more especially the Central African species, are very susceptible.

There is great variation amongst laboratory animals to intracerebral inoculation, and none react so constantly as do white mice. Under laboratory conditions African monkeys (Cercopithecus) are not necessarily immune to the viscerotropic virus, but they do not react by fever and the virus multiplies and circulates in their blood for a short time. Lambert investigated the state of immunity of forest monkeys in parts of Brazil where there had been a human epidemic in 1935. Immune bodies were found in 10·75 per cent. of 1,666 sera collected from 1,153 monkeys and all except two of the 120 immune animals were adults. In another area, where the human disease occurred in 1945, immune bodies were found in monkeys of all ages. These cebus monkeys have a very limited range and yellow fever is seldom fatal in them. The evidence suggests that the infection is spread by infected mosquitoes in the isolated forest patches in the area. It seems therefore that in 1945 yellow fever did not spread in monkeys beyond the areas in which this fever was to be found in man.

The virus can enter the skin of man and through the conjunctiva or nasal mucosa under certain circumstances and cause fatal infections, and has occurred during autopsies on yellow fever cases performed without rubber gloves. Laboratory workers have also become infected by examining monkeys after death. A number of isolated cases have occurred amongst laboratory attendants whilst undertaking blood examination of suspected cases, or whilst working with the virus. These infections, which numbered 35, were due to the pantropic and neurotropic strains (Berry and Kitchen) but, since the introduction of an efficient method of immunization, laboratory infections have entirely ceased.

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Cultivation of the virus.—The virus of yellow fever can be grown solely in the presence of living cells. Haagen and Theiler first succeeded in culturing the neurotropic strain in a medium of minced chicken embryo suspended in a mixture of normal monkey serum and Tyrode solution. Even after a hundred passages there was no appreciable loss of neurotropic activity. Subsequently Lloyd cultivated the pantropic virus (known as pantropic because it produces lesions in all embryonic layers of susceptible vertebrates) which, after more than one hundred subcultures, had become attenuated and could, on this account, be used for protective vaccine. Later still, Elmendorf and Smith grew the pantropic virus on the chorio-allantoic membrane or in the yolk sac of the developing chick embryo, which is the method now universally employed. Strain D-17 of the Rockefeller Institute is such an attenuated virus.

Terms employed for strains of yellow fever virus.—The terms pantropic, viscerotropic, and neurotropic, used in connection with the yellow fever virus, are sometimes rather loosely applied. The naturally-occurring yellow fever virus is pantropic and attacks tissues from all three embryonic layers of the vertebrate host but, when passaged through many series of mouse brains, it acquires affinity for nervous tissue and becomes the neurotropic strain. The viscerotropic, on the other hand, is one which has developed special affinity for organs other than the nervous system, particularly the liver, and it is produced by passage through the liver of rhesus monkeys. Sometimes, however, these strains are reversible and the viscerotropic will still cause a fatal encephalitis when introduced into the monkey brain, the liver being at the same time protected by a parenteral dose of immune serum. Some pantropic viruses from jungle yellow fever in South America have been found to be weak in both neurotropic and viscerotropic affinities, so that it is considered possible that both these could be enhanced by passage through mouse brain or monkey liver respectively.

The neurotropic strain of yellow fever virus.—Once the virus has become fixed for mouse brain it can be passaged indefinitely by intracerebral inoculation in these animals and subsequently, when injected intraperitoneally, it fails to kill. It causes meningo-encephalitis, not only in mice, but also to a lesser degree in guinea-pigs, agoutis, squirrels, peccaries, capybaras, coatis and field voles, as well as all species of monkey, and as a rule, viscerotropic lesions are not produced. Rats, rabbits, hamsters, pigeons, hens and canaries do not develop encephalitis. In hedgehogs, however, intra-cerebral inoculation may be followed by liver necrosis and by nervous lesions.

Physical properties of the virus.—The virus, both neurotropic and viscerotropic, passes readily through ordinary filters, Berkefeld, Chamberland and Seitz. Findlay and Broom, by filtration through graded collodion membranes, have shown that its approximate size is between 18 and 27 m μ . Both the viscerotropic and neurotropic strains of virus are inactivated at a temperature of 60° to 65° C. When dried and frozen, the virus can retain its vitality for many years. It is inactivated by the photo-dynamic action of such dyes as methylene blue (1 in 100,000) and proflavine (1 in 50,000). The pantropic can withstand strong disinfectants, such as mercuric chloride, 1 in 7500, and phenol, 1 in 150, at 30° C. All strains carry a negative electrical charge at the pH of the tissues.

Protection tests as an index of endemicity.—The fact that, after an attack of yellow fever, immune bodies are present in the serum for the remainder of the patient's life, and that, when a mixture of immune serum and

yellow fever virus is injected into susceptible animals, infection does not take place, suggested the practical application of "protection tests" for the diagnosis of recovered cases of yellow fever. When a mixture of the pantropic virus and the serum under examination is injected into a rhesus monkey, if the serum contains immune bodies, the animal does not die. This is known as the "monkey-protection test."

When, however, the neurotropic virus is employed, a mixture of the serum and infected mouse brain is injected intraperitoneally into mice which are simultaneously inoculated intracerebrally with starch. If the serum contains immune bodies encephalitis does not ensue. known as the "mouse-protection test." Both tests possess a high degree of specificity, and results obtained by the two in the same areas of Africa and South America are in close agreement. The mouse protection test is now universally employed and has recently been simplified by modifications introduced by Whitman (1943). This is based on the greater susceptibility of immature white mice to extraneural injection of yellow fever virus. In mice between 18 to 21 days the degree of susceptibility is such that uniform death may be produced by injecting one tenth of the virus dosage required for adult mice without the need for intracerebral injection of starch. In these immature mice, when two parts of immune serum are added to one part of virus, the results of injecting 0.06 ml. of the mixture are equivalent to injecting adult mice, which have received intracerebral starch, with 0.6 ml. This obviously permits satisfactory tests to be made on much smaller serum samples than those required for standard tests.

The technique is as follows. Mice are injected with filtrates of 10 per cent, mouse brain virus. Three days later the brains are removed and emulsified in 15-20 per cent. suspension in saline and subsequently centrifuged at high speed for 40 minutes. The sera to be tested are measured into tubes in quantities of 0.4 ml. each; 0.2 ml. of virus is inserted into each tube of test sera and immune controls.

By this test it has been found that, both in Africa and South America, the areas which have been infected with yellow fever during the lifetime of the present generation are much more extensive than had been previously imagined. Despite the non-recognition of outbreaks of clinical yellow fever in native populations, it has been found in Northern Nigeria, for instance, that 30-4 per cent. of sera are positive. Somewhat similar results have been obtained from French West Africa and the Southern Sudan. There is some evidence that the immune bodies may pass from mother to child by the placenta and also by the milk. In Africa mothers commonly suckle their young for two or three years; this may explain why yellow fever in children is asymptomatic, the children being bitten by an infected mosquito, while their blood contains immune bodies. Monkeys born of immune mothers possess immune bodies in their serum at birth.

Transmission of the virus through the mosquito.—The virus multiplies in the insect vector during a variable extrinsic period. During this period the mosquito is not capable of transmitting the virus by its bite.

In Aëdes ægypti it ranges from 4 days at 98-6° F. (87° C.) and 12 days at 78-8° F. (26° C.) to 18 days at 69-8° F. (21° C.). Under natural conditions the percentage of mosquitoes becoming infected is small. Possibly this may be explained by the small quantity of blood (0·01 ml.) imbibed by Aēdes ægypti. There is no proof that the virus is hereditarily transmitted through the mosquito. Factors concerned in the capacity of a mosquito to transmit yellow fever are: (1) the fate of the virus, and (2) the degree of contact between it and susceptible vertebrates. Thus it comes about that many species may harbour the virus for long periods but are incapable of transmitting.

At 10-18°C. the virus can persist in the insect's body for a long time without being capable of transmission, but at 28°C. for one week this becomes possible. At 37°C. this can occur in four days (Davis). In the S. American species¹ Hæmagogus spegazzinii falco the extrinsic incubation period is markedly affected by temperature. This indicates that as the mosquito is placed in a progressively less favourable environment it becomes less suitable for the virus. Serial passage of virus strains through mouse brains or chick embryo results in a type poorly adapted for development in mosquitoes. When the virus content of the bloodstream of an infected animal is 100 M.D. for mice per 0-03 ml. it is unusual for a single mosquito to become infected, but as the virus content of the blood rises beyond 10,000 M.D., the percentage of infected mosquitoes rises rapidly. It is amongst those insects which breed in tree holes that the bulk of yellow fever vectors are found. There is evidence that immune serum can neutralize virus in the stomach of the mosquito.

The question of vertical distribution has an important bearing on the contact of a species of mosquito with arboreal as opposed to terrestrial vertebrates. In contrast to the midday activities of the Hæmagogus genus is the sharply restricted activity of Aëdes africanus. This mosquito confines its major feeding period to about one hour of the day, after sunset, but before complete darkness has set in.

It has been shown that A. ægypti in Brazil has a flying range of 120 metres. By using radioactive phosphorus and strontium for marking mosquitoes Burgher and Taylor were able to show that they are distributed largely by wind drift rather than by their own flight. A. ægypti, which is a domestic species in S. America and W. Africa, in the Bwamba country area in Uganda is quite different in life habits, so that it is virtually incapable of aiding in the spread of yellow fever. A. africanus can transmit yellow fever in nature. A. simpsoni, which has a wide distribution throughout Africa, behaves differently in Bwamba country where it breeds in plant axils, especially bananas and colocasia. In forest areas it replaces A. ægypti as vector of yellow fever virus. Tæmorhynchus africanus is the commonest arboreal mosquito in forest canopy, but there is no actual evidence that it transmits yellow fever in nature.

In S. America mosquitoes of genus *Hæmagogus* and *Aëdes leucocelænus* have a pattern of daytime feeding which brings them into contact with man as well as with monkeys.

¹ The commonest species *H. spegazzinii* can only be distinguished from the other proven vector of sylvan yellow fever—*H. capricornii*—by the male gentalia.

Observations on the habits of A. ægypti indicate that the female does not lay eggs until she has fed on blood, and that these are deposited three days after feeding. At this stage she is especially susceptible to infection with the yellow fever virus (see also p. 335). The course of development of the virus in the mosquito has not been traced. The type of development appears to be simple for, if infective mosquitoes are ground up and fed in syrup to normal A. ægypti, they too become infective after the usual extrinsic period. It has been shown that the virus undergoes multiplication in the mosquito and that it is present in its alimentary canal for at least ten days after an infective meal. Subsequently, it becomes centred in the salivary glands.

Species of mosquito, other than A. ægypti, capable of transmitting the virus. —In South America jungle yellow fever occurs in the absence of A. ægypti. Other species have been found infected: Aēdes leucocelænus, Hæmagogus spegazzinii falco and some sabethinæ. In Bwamba, Uganda Aēdes simpsoni has been proved to be the vector of jungle yellow fever. Another species, A. africanus bites at night and feeds on monkeys at 80 ft. above the ground. The jungle species of mosquito vectors are usually inhabitants of the tree tops and rarely descend to ground level, and it has been shown that some infected Hæmagogus have never been in contact with man at all. In the Southern Sudan Tæmiorhynchus africanus has been suggested as the vector and in the Nuba Mountains epidemic Aëdes vittatus and A. metallicus were probably the vectors.

The following have been found capable of transmitting yellow fever virus by bite under laboratory conditions, but probably not all do so

naturally:-

South American mosquitoes: Aëdes ægypti, A. fluviatilis, A. leucocelænus, A. scapularis, Hæmagogus capricornii, H. spegazzinii (H. s. falco), H. equinus, H. splendens, transmit virus.

The following are susceptible: Aedes nubilus, A. serratus, A. terrens, A. fulvithorax, A. tæniorhynchus, Hæmagogus uriartei, H. tropicalis, Psorophora ferox, P. cingulata, Tæniorhynchus albicosta, T. chrysonotum, T. fasciolata, T. justamansonia, T. titillans, Wyeoniyia bromeliarum, Culex fatigans, C. nigripalpus.

A. leucocelænus is widespread and plays an important part in the spread of yellow fever. Hæmagogus are tree-hole breeders and feed on marmosets. Yellow fever virus is isolated from the genus Sabethoides, which are difficult to keep in laboratory. Trichoprosopon frontosus is a species belonging to thegenus Gældia a sabethine which can transmit in laboratory and is widespread.

African mosquitoes: Aëdes ægypti, A. africanus, A. luteocephalus, A. metallicus, A. simpsoni, A. vittatus, A. stokesi (apiocannulatus), A. taylori, Eretmapodites chrysogaster, Culex thalassius:

The following are susceptible: Tæniorhynchus uniformis, Aëdes cumminsi, A. irritans, A. nigricephalus, A. lineatopennis, A. punctocostalis.

Mattingly found in S. Nigeria, as in Uganda, that Aëdes africanus bites mainly at tree-top level and in the evening twilight. This mosquito was

first implicated by Haddow and colleagues in the forest cycle of yellow fever in Uganda. The virus was obtained from a batch caught in nature. Monkeys were exposed on platforms at canopy level in the forest; only one out of 39 became infected.

General observations.—The observations which have been made upon the ætiology of yellow fever appear to explain some generally accepted facts.

(1) The impunity with which a yellow fever patient can be visited by

a non-immune person, if outside the endemic area.

(2) The danger of visiting the endemic area when mosquitoes are both active and infective. A. agypti usually feeds in the late afternoon, though this does not hold good in the case of jungle yellow fever, where the forest-living mosquitoes in South America and Central Africa bite during the day time.

(3) The discrepancy between the incubation period of the disease, three to five days, and the period, fourteen days and over, between batches of cases. The evolution of the virus in the mosquitoes infected by the original patient demands the space of time indicated by the difference

between these periods.

(4) The clinging of yellow fever infection to ships, buildings and localities. This is due to the persistence of the virus in infected mosquitoes (Aēdes egypti) which are now known to be capable of surviving for five months, possibly longer, after feeding on human blood.

(5) The higher atmospheric temperature required for the epidemic extension of yellow fever. Such temperature favours the activities of the mosquito and is necessary for the multiplication of the virus in the insect.

Biochemical changes produced by the virus.—All the biochemical changes which occur in yellow fever can be interpreted as an interference with the liver and kidneys. Thus, there is loss of glycogen from the liver and a considerable reduction in the blood-sugar. Findlay and Hindle showed also that, as in other toxic affections of the liver, there is, in rhesus monkeys and in humans, an increase in the blood of guanidine-like substances. The repeated administration of calcium lactate in large doses reduces this excess of guanidine and may play a part in preventing gastric hæmorrhage. The hæmorrhages, however, are largely due to the loss of vitamin K following liver necrosis.

Pathology.—The pathological appearances vary very greatly with the clinical course of the disease. In typical cases the olive-yellow colour of the skin is most marked in the dependent parts of the cadaver, especially in parts subjected to pressure. Rigor mortis is pronounced. Petechiæ are common in the skin and serous membranes; more considerable extravasations of blood may be found in the muscles. The brain and meninges are hyperæmic and may be studded with minute effusions; like the other tissues of the body, they may be stained a lighter or deeper yellow. The cartilages are intensely yellow. Intensive hæmorrhagic lesions have been observed in the lungs in 90 per cent. of cases (Klotz and Belt).

The blood in the vessels of the general circulation is not firmly coagulated. An important fact, explaining the liability to passive hæmorrhages, is

the existence of a generalized fatty degeneration of the capillaries and smaller blood-vessels. The stomach usually contains black or fluid blood. The folds of the gastric mucous membrane are swollen and there are arborescent patches of ecchymosis. The small intestine contains a dark material similar to that in the stomach. Only after microscopic examination of the organs, especially the liver, can a pathological diagnosis of

vellow fever be made.

The virus of yellow fever, like certain other viruses, has a particularly destructive action on the liver cells, and by microscopic examination of liver sections alone it is usually possible to arrive at a diagnosis. In the early stages the liver is red from extravasation of blood, but if death has occurred later, the organ is usually somewhat friable and may present a vellowish colour which has been compared with that of box-wood. The microscopic pathology of the liver is well defined. Necrobiosis and acidophilic necrosis are found in the mid-zonal region of the liver lobules. to a lesser extent at the periphery. Fatty changes are more extensive than the necrosis. The liver cells are often separated one from another and tend to assume a rounded shape; fatty degeneration may be very intense (Fig. 52). The typical lesion is a coagulative necrosis with a marked edge, surrounded by a narrow clear halo. Frequently the cytoplasm, in whole or in part, undergoes a hyaline degeneration—hyaline coagulation necrosis-together with hyaline bodies, first described by Councilman, while the cytoplasm of all the liver cells stains more intensely with acid stains such as eosin. The necrosis of the liver is not exactly a midzonal necrosis, as is often stated, but a scattered necrosis occurring throughout the lobule, giving a salt and pepper appearance in sections stained with hæmatoxylin and eosin. The nuclei of the liver cells exhibit margination of the chromatin round the nuclear membrane, while in some cells the nucleoplasm is occupied by acidophilic intranuclear masses (Fig. 53). Hyperplasia of the Kupffer cells is usually noted. Usually only a small number is affected, but with certain strains 70-80 per cent. exhibit inclusions. In the rhesus monkey a high percentage of cells always shows intranuclear inclusions. These were first described by Torres and specially studied by Cowdry and Kitchen; they are similar in type to, though not identical with, those found in many other virus diseases. Within the liver lobules there is hyperplasia of the endothelial cells of the sinuses and an infiltration with large mononuclear cells and a few polymorphonuclear leucocytes. In the rhesus monkey the infiltrating cells are predominantly polymorphonuclear, while 80-90 per cent. of the parenchymatous cells contain acidophilic intranuclear inclusions. Councilman lesions, on the other hand, are comparatively rare, while fatty degeneration is also less marked than in man. In some epidemics, as in Accra in 1937, the percentage of liver cells containing intranuclear inclusions is high.

In the spleen there are no characteristic changes, but the endothelial cells of the splenic sinuses may show hyperplasia, while the Malpighian corpuscles are somewhat atrophied. Definite changes, however, are found in the kidneys. The reaction is a nephrosis, not a nephritis. Hæmorrhagic foci under the capsule and in the cortex are common. Fatty changes with necrobiosis and necrosis of the tubular epithelium are present. The

tubules, here and there, are filled with casts, either of an albuminoid material or of débris of desquamated epithelium, corresponding with the casts in the albuminous urine. Granular and hyaline casts are found throughout the tubules of both cortex and medulla. Hoffman regarded lime-casts in the convoluted tubules as distinctive of yellow fever. Degenerative changes occur in the heart muscle, including the bundle of His.



Fig. 52.—Yellow fever: section of liver (low power) showing fatty and hyaline degeneration and Councilman lesions. (Dr. G. M. Findlay.)

Although the virus is highly neurotropic, no extensive lesions of the central nervous system are found. Although individual hæmorrhages are small the total blood loss is extensive.

Symptoms.—There is the same variety in the initial symptoms of yellow fever as in other specific fevers. In both urban and jungle yellow fever many mild and clinically unrecognizable cases occur. In the first stage the symptoms may range from an almost imperceptible febrile reaction to severe prostration. Yellow fever in man may be divided into (1) the very mild, (2) mild, (3) moderately severe, and (4) malignant types. In very mild yellow fever the only symptoms are fever and headache which last from a few days to a day or two. This febricula is undiagnosable, even in an epidemic, for unapparent infections occur, especially in endemic areas, as a result of long contact with the virus. Some infections are found in babies who are losing the passive immunity bestowed upon them by their

immune mothers. The *incubation period* is from 3-6 days though considerably longer periods are recorded in accidental infections in which it is from 10-13 days.

Roughly speaking, and provided there are no complications, an attack of yellow fever is divisible into three stages—(1) the initial fever; (2) the "period of calm"; and (3), in severe cases, the period of reaction.

The initial fever is usually sudden in onset, and lasts from three to four days. The maximum temperature is generally attained within the first twenty-four hours, or by the second day, and, in a case of medium severity

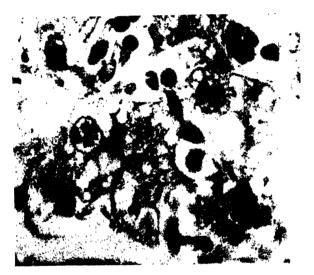


Fig. 53.—Yellow fever: section of liver \times 2,000 showing acidophilic intranuclear inclusions (Torres bodies). (Dr. G. M. Findlay.)

may rise to about 103° or 104° F. During the three or four succeeding days the mercury slowly sinks to 98° or 99° F., the daily fluctuations being seldom more than a half to one degree. It occasionally happens that high temperature is maintained for more than three days, and also that the maximum is not attained until the eighth, but, as a rule, it is reached within two days of the onset (Chart 19).

With, or soon after the initial chill or rigor, severe headache sets in and is generally a prominent feature. For the most part the pain is concentrated about the forehead, in the circumorbital region and in the eyeballs.

In many cases it is associated with intolerance of light.

Loin pain is another very distressing symptom; it may amount to positive agony; the backache may be as bad as in a severe case of small-pox. The legs, too, ache excessively—particularly the calves, knees, and ankles; they feel as if broken. Epigastric pain is generally prominent.

The face is flushed and swollen; the eyes are shining, injected, and ferrety; the skin is dry.

What with pains and febrile distress, the patient passes into a very miserable condition. He is restless and continually tossing about.

At first the pulse ranges from 100 to 120, and is full and strong; but as the disease progresses, the pulse loses its sthenic character, gradually falling in force and frequency until, at the "period of calm," it becomes remarkably slow and compressible, beating perhaps only 30 or 40 times per minute. This fact may be of particular value in diagnosis, and is known as Faget's sign—that is, a falling pulse-rate with a constant temperature, or a constant pulse-rate with a rising temperature. It is in fact

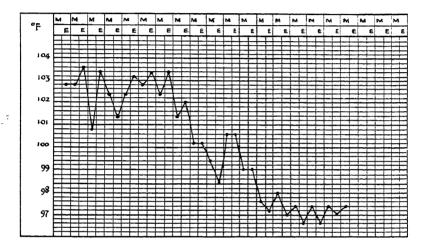


Chart 19.-Laboratory infection of yellow fever. Recovery.

a sign which emphasizes the lack of correlation of temperature and pulse, so that by the second day, notwithstanding the high temperature, the pulse-rate becomes slower, and by the third or fourth day it has probably decreased 20-40 beats from its initial rate. As a prognostic sign—a quickening pulse rate with a falling temperature indicate that death is near.

At the outset the tongue is not very dirty, but it soon acquires a white coating on the dorsum, the edges remaining clean. It is not so swollen and flabby as in malarial fever; on the contrary, it is rather small and pointed throughout the disease. This is regarded as an important diagnostic mark; taken along with the progressive diminution in the strength and frequency of the pulse and the peculiar behaviour of the temperature, it is nearly conclusive of yellow fever. Later, the tongue dries and, at the same time, thirst becomes intolerable. The palate is congested and swollen; the gums may also swell and bleed.

The congested appearance of the face at the onset of the disease tends to subside; so that by the time the asthenic stage is reached the features may have become small, the eyes sunken, and the eyelids discoloured by ecchymoses.

In some cases the skin is hot and dry throughout; in others it may be bedewed with perspiration from time to time; or the sweating may be

constant, especially if collapse sets in.

By the third day the scleræ assume a yellowish tinge, and very often the skin acquires that yellow colour from which the disease derives its name. In severe cases bluish spots may be observed and are due to subcutaneous hæmorrhagic effusions. It must not be understood, however, that every case presents this colour of skin; in some it is entirely absent, but if carefully looked for there is always some yellowness of the scleræ. The yellow tinging of the skin generally shows about the end of the first stage, deepening in intensity as the case advances, and remaining apparent for a considerable time after convalescence has become established. It ranges in depth from a light saffron to a deep mahogany brown. In fatal cases it is always present—not necessarily during life, but invariably after death. The skin in bad cases is said to emit a peculiar odour like gunwashings, or, as Jackson puts it, like the smell of a fish-market.

Petechial, erythematous, papular, and other eruptions may show themselves in different cases; but in yellow fever there is no characteristic eruption, unless it be an erythematous congestion of scrotum or vulva, which occurs in a proportion of cases and is described as diagnostic.

An important feature, from the diagnostic as well as from the prognostic point of view, is the appearance, in some cases almost from the outset. of albumin in the urine, together with a tendency to suppres-At first urine is abundant, but chlorides diminish rapidly, and suppression, according to Pichat, appears towards the end of the second day. In mild cases these changes may be little marked; but in severe cases, particularly during the stage of depression, the urine may fall to a few ounces, and be loaded with albumin to the extent of one-half or even twothirds (usually about 2 grm. of albumin per litre). The more pronounced these symptoms, the graver the prognosis. The amount of albumin increases as the temperature falls. Urea (even during the incubation period) and uric acid are very much diminished, the former in severe cases falling to 1.5 grm. to the litre. The urine is almost invariably acid, depositing granular casts, and sometimes giving spectroscopic evidence of hæmoglobin. Bile-pigments and bile-stained tube-casts show themselves towards the end of the disease, usually about the fifth day, and their appearance is regarded as a favourable omen. Peptonuria indicates a serious prognosis. The blood urea is usually high during the terminal stages.

Insomnia is usual, but if it occurs before the third day prognosis is said to be grave. Delirium may occur, but is not invariable. Usually, after the initial stage of restlessness and acute suffering, the patient becomes torpid, and perhaps tacitum. In bad cases come and subsultus may gradually supervene, the temperature rising as death approaches, and even after. A well-marked tache is present on the forehead, as well as on other

parts of the body.

At the outset the bowels are confined. In the second stage, diarrhea, perhaps of black material resembling the vomit, may supervene; or there may be actual hæmorrhage of bright-red blood from the bowel.

Nausea and vomiting are more common than in other fevers. The well-

known black vomit—always a grave symptom, but fortunately not by any means an invariable one—forms one of the most striking features of this disease. In the earlier stages of the fever, vomiting of bilious matter is common. This may subside or, after a time, give place to "coffee-grounds" which seem to gush up without straining or effort on the patient's part, and which gradually deepen in colour until they become uniformly black. On microscopical examination the vomited material is found to consist of broken-down blood-corpuscles and altered hæmoglobin suspended in a yellowish mucoid fluid. This material is, doubtless, in the main derived from blood transuded through the walls of the capillaries of the mucous membrane of the stomach. It is intensely acid. Though the black vomit may not always be seen in fatal cases during life, the material is invariably found in the stomach post mortem.

Sometimes pure blood is thrown up from the stomach; similar passive hæmorrhages may take place from almost any part of the body—from eyes, ears, nose, mouth, bladder, uterus and so on. "Everything is congested at the outset, everything bleeds at the end," is a well-known adage.

Death may occur during the early acute stage, being preceded by a rapid rise of temperature. The majority of deaths occur on the fifth and sixth days; the end seldom comes before the third or after the eleventh day, and, at this stage, is generally preceded by a rapid fall of temperature.

In mild cases the "period of calm," which sets in after the subsidence of the initial fever, may last for several days before convalescence. The most constant symptoms are headache, pain in the back and extremities, photophobia, anorexia, prostration, congestion of the eyes, with a typical tongue, pointed and coated, but with red edges and tip. In such cases, recovery, once begun, is usually rapid; in a week from the beginning of the disease the patient may be about again. In severe cases, however, the period of calm is followed by a third stage, the stage of reaction, in which the temperature again rises, though not to so high a point as in the initial fever, and a sort of remitting fever of an adynamic type keeps on for several days or weeks. This secondary fever is more prolonged if there is any complication. such as abscess, boils, parotitis, buboes, or secondary hepatitis. The icterus is now very pronounced; black vomit may recur, or appear for the first time: perhaps a profuse diarrhœa ends in collapse; or the urine may be suppressed, stupor, coma, and other nervous symptoms ensuing, and very often ending in death. In other instances the secondary fever terminates in a crisis of sweating and prolonged convalescence.

Even in Europeans, as illustrated by certain of the infections contracted in the laboratory, yellow fever may be comparatively mild and may resemble an attack of influenza.

Relapses are unknown. The immunity produced by one attack of yellow fever is usually permanent, as permanent as that produced by smallpox or measles.

As a rule there is no anæmia, but there is a slight leucocytosis early in the disease, soon followed by a leucopenia, which reaches its lowest point about the fifth or sixth day (Berry and Kitchen); the polymorphonuclear leucocytes are not increased, but there is an increase of mononuclear cells during convalescence. In human infections the virus has been shown to

exist in the blood 107 hours after the onset of fever, while antibody has been detected after 83 hours, thus confirming what had already been suspected on epidemiological grounds of the simultaneous presence of virus and antibody in human blood in yellow fever. In icteric cases the Van den Bergh reaction is biphasic.

The overall fatality rate in yellow fever lies between 5-10 per cent. of all cases, but this rate may rise above these limits in a given epidemic.

Complications and sequelæ.—Suppurative parotitis (usually unilateral) is the most striking complication, but lobar pneumonia is more serious and myocardial failure after apparent complete recovery constitutes a definite hazard.

Experimental yellow fever infection in monkeys leads to a febrile reaction which is not high during the early days of the illness, but subsequently there is a sudden rise of temperature followed by a rapid fall and the animal dies in coma. In some there is an alternating rise and fall and in others a rapid crisis and death. Death may take place as early as the fourth or as late as the fifteenth day.

Diagnosis and differential diagnosis.—Routine urine examination must be carried out in all febrile cases and all with a greater degree of albuminuria than is justified by the degree of fever should be considered suspect. Other points to be considered are the severity of initial symptoms. the relation of pulse and temperature at different stages of the disease. the degree and colour of the jaundice, the time of the appearance and the occurrence of hæmorrhages. Severe yellow fever may be confused with remittent subtertian malaria, Weil's disease, infective hepatitis, relapsing fever, and blackwater fever. The difficulties of clinical diagnosis are often great, especially early in an epidemic. When several deaths. preceded by fever and black vomit, have occurred within a limited area and in quick succession, a suspicion of yellow fever should be entertained, though sometimes this has been observed in Weil's disease and in relapsing fever as well as in outbreaks of infective hepatitis. There is no clinical feature, so far as is known, which would distinguish a mild attack of yellow fever from an ordinary febricula, nor any pathognomonic clinical sign that would absolutely distinguish a malarial remittent from yellow fever and from Weil's disease, though in the latter there is usually a polymorphonuclear leucocytosis. Dengue is probably one of the most difficult diseases to differentiate from mild yellow fever. The facies, orbital pains, and backache are similar to those of dengue, but the appearance of the characteristic eruption of the latter disease on the fourth day should settle the diagnosis in any doubtful isolated case. Probabilities must be weighed in diagnosis when it is based on clinical grounds alone. The only reliable guides, as between malarial and yellow fever, are the discovery of the malaria parasite, the characteristic pigment and leucocytic variation in the one, and the determination of their absence in the other, but in an area where mclaria is endemic, the finding of parasites does not rule out concomitant yellow fever. Post morten, the presence of pigment in the viscera in malaria, and of extensive necrosis of the liver-cells in yellow fever, is diagnostic. Biopsy of liver tissue by the special trocar will probably be of value in doubtful cases. Occasionally the two diseases

may co-exist. The presence of albuminuria is of value in early and abortive cases, especially in Europeans, but albuminuria is more easily provoked in West Africans from any cause.

In addition to the diseases mentioned, there is great difficulty clinically in diagnosing yellow fever from Rift Valley fever, or, in its milder manifestations, from some forms of influenza, especially of a virulent strain. Occasionally relapsing fever may assume a malignant form with intense icterus and resemble yellow fever in its clinical manifestations, but it may be distinguished by leucocytosis, splenomegaly and spirochætes in the blood. Smallpox, in the first three days, before the rash, may be very similar to yellow fever.

It must also be remembered that in adults infective hepatitis may occur in severe form, while unexplained outbreaks of fever and jaundice, not due to the yellow-fever virus, have been described (see p. 355). In epidemics of infective hepatitis the jaundice is usually deeper than in yellow fever and the patient may be afebrile. These diseases have been differentiated by failure to infect rhesus monkeys during the acute stage, and by the absence of immune bodies to yellow fever in the blood. In West African natives, particularly, jaundice and albuminuria are common accompaniments of lobar pneumonia and relapsing fever. An acute sickling crisis in an African may produce severe jaundice, which is also seen in staphylococcal and meningococcal infectons.

Laboratory diagnosis.—With modern advances in our knowledge of the ætiology of yellow fever an increasing confidence is being felt in its diagnosis. The virus may be isolated from the blood in the early stages, preferably during the first three days. A venule type of vacuum syringe should be used. The specimen should be kept cool, but never frozen; and the serum which should contain no hæmoglobin, must be inoculated subcutaneously into a non-immune monkey or intracerebrally into white mice of a susceptible strain. The development of specific antibody to yellow fever in the serum can be demonstrated by the mouse protection test.

In fatal cases yellow fever may be diagnosed post mortem from a histological examination of the liver, the essential features being the fatty degeneration, mid-zonal necrosis, infiltration with mononuclear cells, and the presence of Councilman lesions (hyaline bodies) and acidophilic intranuclear inclusions. The employment by the International Health Division of the Rockefeller Foundation of the "viscerotome" enables portions of liver to be removed from a cadaver without a general post-mortem examination. An examination of the livers of all those who have died from acute disease has, in South America, enabled many unsuspected cases of yellow fever to be accurately diagnosed, and there is now a well-organized viscerotome service.

In any outbreak of febrile illness with jaundice in an area where the mosquito fauna would permit yellow fever to spread it is important that serum from patients in the early stages of the disease and from the same patients when convalescent should be examined for yellow fever protective bodies. and liver tissue of cadavers for the appearances typical of yellow fever. By these means, in countries hitherto not invaded by yellow fever, early information may be gained and steps can be taken to control the disease.

Complement fixation.—Attempts have been made to discover some simple test for yellow fever which would obviate the more elaborate protective tests in experimental animals. Davis, Frobisher and Hudson have made numerous experiments using, as an antigen, either plasma, serum or liver optomed from

monkeys on the first or second day of fever, while more recently infected yolk sac has been employed. The concentration of complement-fixing bodies has been found to reach its maximum in monkeys after thirty to forty days, and they remain in the circulation for a few months to more than one year.

Prognosis and mortality.—Prolonged initial rigors, algidity. convulsions, suppression of urine, coma and hæmorrhages are all unfavourable symptoms. The prognosis is good if the temperature during the initial fever does not exceed 103° to 105° F. It is better for women (although, if pregnant, abortion is almost invariable) and children than for men: better for old residents than for newcomers; worst of all for the intemperate. According to a table given by Sternberg of 269 carefully observed cases. there were no deaths in 44 in which the temperature did not rise over 103° F.: in 22 cases in which the thermometer rose to over 106° F. there were no recoveries. The mean mortality in the whole 269 cases was 27.7 per cent. In some epidemics it has risen as high as 50 or even 80 per cent. of those attacked, but between 25 and 30 per cent. may be taken as a fairly representative mortality among the unimmunized. Among the permanent inhabitants of the endemic districts the case-mortality is very much lower-7 to 10 per cent. In the outbreak in the Sudan it was about that figure. During epidemics, abortive and ambulatory cases occur; in these, icterus and other characteristic symptoms are often absent. Such cases may be hard to diagnose from febricula or mild malarial attacks, and the mortality is nil. Some epidemics are particularly mild: in others, the majority of the patients die. In the same epidemic the cases may vary in severity from time to time. In children the mortality is low.

TREATMENT

Formerly a much more active treatment than that in vogue at the present day was the fashion for yellow fever. It is now recognized that, as with most virus diseases, the treatment is more a matter of nursing than of drugs. Once in bed, the patient should not be allowed to get up. As in other virus diseases the injection of immune serum is valueless once the infection has begun; given during the incubation period, however, it may prevent, or at any rate decrease, the severity of the disease. Since the virus is efficiently neutralized by the formation of immune serum by the third or fourth day after the onset of fever, it follows that death is caused by the destructive effect of metabolic toxins on the liver, heart and kidneys.

Experience has shown that a smart purgative at the very onset of the disease may be beneficial. With many, castor oil is the favourite drug, but to be of service it has to be given in very large doses—2 oz. or more. Others use calomel, or calomel combined with quinine. Others, again, prefer a saline purge.

Hot mustard plasters, frequently repeated during the first twenty-four hours, are much in favour. They are said to relieve the cerebral congestion and the intense headache. Hot baths, with subsequent blanketing and sinapisms to the epigastrium, are said to have a similarly favourable influence on the congestion of the stomach, which is, undoubtedly, another

constant feature. For high fever, antipyretic drugs, cold baths, iced injections, cold sponging and the like may be carefully employed. In view of the asthenic nature of the disease the less depressing measures should be preferred. In severe cases intravenous injections of casein hydrolysates might be of value as they have produced miraculous cures in cases of liver necrosis due to carbon tetrachloride and in infective hepatitis. Doses of

vitamin K are of value in preventing hemorrhage.

Vomiting may be treated with ice pills, or with small doses of cocaine. Luminal is indicated to induce sleep in restless cases, and codeine sulphate to relieve headache and backache. For black vomit, frequent doses of perchloride of iron, ergotine injections and acetate of lead have been recommended. Calcium lactate, in large and repeated doses by mouth, is probably of value in counteracting the excess of guanidine in the blood. The administration of glucose in the treatment of the hepatic conditions represents a distinct advance, and good results from this line of therapy have been reported. Glucose should be given in drachm doses, whenever feasible or, when nausea is present, in 5 per cent. solution intravenously (10 oz.), while injections of 5 units of insulin improve its assimilation. For restlessness, phenacetin or antipyrin is used. When the skin is dry, the urine scanty, and the loins ache excessively, Sternberg recommended pilocarpine.

After the fourth or fifth day the flagging circulation demands stimulants of some sort. Iced champagne, hock, or teaspoonful doses of brandy, given every half-hour, may tide the patient over the period of collapse. Great care, however, should be exercised in the use of these things; if they seem to increase the vomiting and the irritability of the stomach they must be

stopped at once.

Free ingestion of water and alkalis tend to obviate failure of renal

function, which is the usual form of death.

The feeding is important. So long as there is fever the patient has no appetite; during this time—that is, for the first two or three days—he is better without food. When the fever subsides appetite may return, and a craving for nourishment becomes more or less urgent; the greatest care, however, must be exercised about gratifying this untimely appetite. Protein in the diet is of value in protecting the liver from damage. Gradually the quantities may be increased; but, even when convalescence is established, solid food must be taken very sparingly, and must be of the simplest and most digestible kind. Indiscretion in eating is a fruitful cause of relapse in yellow fever, which may be exceedingly dangerous. Nutrition may be aided by nutrient enemata. Any slight exertion which may cause a rise in blood-pressure may be fatal. It is possible, too, that stimulation of the circulation incident to the taking of food explains the dangers of altering food during the early stages.

Any suspected case of yellow fever should be nursed under a mosquito-

net day and night, and preferably in a mosquito-proof room.

Prophylaxis.—A period of six days' quarantine is now accepted by the international sanitary convention as necessary after exposure to infection. It is the duty of sanitary authorities in tropical countries to free the areas over which they have charge from Aëdes æqypti mosquitoes as far as possible. Although complete destruction is not to be expected, relative extermination of mosquitoes is worth attempting, and certainly can be attained by the vigorous use of the now well-known measures. In Havana, by such means, in a very few months the number of mosquitoes was reduced by 90 per cent., with a corresponding gain to the community in the diminution of mosquito-conveyed disease. The same has happened in Panama, Rio de Janeiro and elsewhere in S. America by residual DDT spraying.

All water-tanks, gutters, and cisterns must be effectually screened against Aēdes æqypti by fine-meshed metallic gauze; discarded tins should be collected and rolled out by steam rollers; all puddles and stagnant water must be abolished and all holes in trees should be closed or the trees felled. Roof gutters are best abolished altogether. In Africa special attention must be paid to the control of mosquito-breeding on native dhows. For other insecticidal sprays and the use of DDT in combating

yellow fever (see p. 861).

Any delay in recognizing the earliest cases of a threatened epidemic is, as shown by experience in New Orleans, most dangerous, leading, as it may, to the rapid multiplication of infected centres.

Ships should not be allowed to clear from infected ports, nor to enter non-infected ports, during the hot season, without adequate inspection.

Aircraft.—It is necessary, in view of the increasing facilities of air travel, to immunize all those proceeding from an endemic to a non-endemic area. It has been recommended by International authorities that measures for preventing spread by aerial traffic should be taken primarily before departure from areas where the disease exists, and only secondarily at ports of arrival. Measures to be taken before departure include freedom of crews and passengers from any risk of infection during six days before embarkation and freedom of aircraft and cargo from the possibility of conveying mosquitoes. It is recommended that the International Civil Aviation organization should take sanitary control of all airfields which might be involved in the spread of disease, control disinsectization of aircraft, control the storage, testing and injection of yellow fever vaccine and control the issue of yellow fever inoculation certificates. considerations should modify the tendency to alarmist views of the danger of importing the yellow-fever virus to Eastern countries, such as India or China, where the disease is so far unknown, but where climatic and hygienic conditions are favourable to its spread. One of these is the ease with which aerodromes can be kept free from yellow-fever mosquitoes, as well as the ease and rapidity with which aircraft can be freed.

In the United States it has been proved conclusively that Aëdes ægypti can be carried by aircraft for long distances, and the necessity of destroying these insects is insisted upon in all aeroplanes flying in tropical countries. Aircraft should be sprayed on the ground prior to departure. Disinsectization is best carried out by dispersing the insecticide in a low-boiling solvent. "Freon" (Freon = dichlorodifluoromethane and a refrigerating agent) is a low-boiling solvent. Little equipment is needed for the production of aerosols by this method, but the container must have a liquid delivery

tube extending to the bottom, since the solution, not the gas, is to be sprayed. Only a small orifice is used so that no expansion takes place until the solution is sprayed into the atmosphere. Aerosols produced by this method are much more finely divided than the mists produced by most spraying methods and settle more slowly. Disinsectization can be effectively carried out in 5–10 minutes.

An aircraft should be regarded as infected with yellow fever, if there is on board any person who within ten days of arrival has been in a yellow fever infected area, and who has not been inoculated against yellow fever for more than ten days prior to arrival.

If a person has alighted from a yellow fever area at a non-infected aerodrome and is in possession of a certificate from the Health Office of that aerodrome stating that, during his stay, he either remained within the non-infected aerodrome, or, if he went outside it, he did so under such protected conditions as would make it impossible for him to be bitten by mosquitoes, he may be permitted to proceed; more especially if he has been protected against the disease by a previous attack or by satisfactory inoculation.

The rules of the International Sanitary Convention must be consulted.

There is danger that, with increased motor traffic and better road communications, infected persons will be able to travel from endemic to non-endemic areas in a time well within the incubation period of the disease. All motor traffic from endemic to non-endemic areas has, therefore, to be carefully regulated.

Prophylactic inoculation has been practised since 1931 in West Africa, Brazil, Colombia and South America generally.

During the first six months of 1942, 28,585 cases of jaundice appeared in American troops who had been injected with this yellow fever vaccine prepared by the Rockefeller Institute, and 62 died of acute necrosis of the liver. Similar accidents have supervened after injection of measles and mumps convalescent serum and also after whole-blood transfusion with an incubation period of about 16 weeks. The agent responsible for the jaundice is present in the nasal washings and serum from patients in the pre-icteric and possibly also in the icteric stage (Findlay and Martin, 1948). The addition of human serum has therefore now been omitted and no further cases of jaundice have occurred.

Reaction immediately following inoculation with the attenuated pantropic virus is either lacking or consists of slight headache for forty-eight hours. After immunization, immune bodies appear in the serum from the twelfth to fourteenth day, and reach their maximum about the twenty-first. In many immune bodies are detectable for seven years or longer by the mouse-protection test. It is advisable that the blood of immunized persons should be tested every two or three years and, if necessary, they should be re-inoculated. With certain batches of vaccine made from virus 17 D, Fox and others have reported a few cases of encephalitis. This complication appeared suddenly in 1941. 17 D virus (Asibi strain) is distinguished by marked attenuation. When inoculated intracere brally into rhesus monkeys it causes encephalitis—which is not usually fatal.

The more viscerotropic the strain the higher is the concentration of the virus in the liver.

A ralid inoculation certificate is one certifying that the bearer has been inoculated for the first time more than ten days and less than five years previously to entering the endemic zone, or that he has recovered from an attack of yellow fever and his blood contains immune bodies.

On the whole, results have been very satisfactory. Very few deaths from yellow fever have been recorded in inoculated individuals, though not all are equally protected. Aëdes mosquitoes are unable to take up the virus from the blood after immunization, so that there is no reason why protective inoculation should not be carried out in areas where these insects are present. Mass inoculation is the only practical answer to the jungle yellow fever problem, as was amply demonstrated by the vaccination of over a million persons in Brazil in 1938. During the recent war nearly quarter of a million troops in West Africa were immunized by the 17 D virus.

Similar steps have not yet been taken by the authorities in British East and West African territories and the Anglo-Egyptian Sudan to ensure that mass inoculation is done in Europeans and in indigenous inhabitants.

Preparation of yellow-fever vaccine.—Because the concentration of the virus in tissue culture is never very high, developing chick embryos, about seven days old, are inoculated with tissue culture virus, 17 D, 0.05 ml. Aqueousbase vaccine is now employed (Hargett). A small hole is drilled through the shell, and after inoculation this is sealed, and eggs returned to the incubator for a further 90 hours. The embryos are then triturated and for each 3 grm. is added 1 ml. of distilled water. The finely-divided tissue extract is centrifuged for 30 minutes at 3,500 r.p.m. and the supernatant fluid drawn off. The filtrate. which is used for inoculation, usually contains between 1,000 and 10,000 mouse minimal lethal doses of virus per ml. Yellow-fever virus is very labile, and rapidly becomes inactivated in liquid state, even when kept in the icebox, but when desiccated in frozen state in vacuo it is much more stable. preparations are therefore dried in the frozen state and sealed in glass after desiccation. When the residual moisture is low, and the material is kept in the icebox, the virus remains active and virulent for years. If, however, the residual moisture is over 5 per cent. the keeping qualities are reduced. constitutes one of the chief difficulties in the application of the present type of vaccine for large-scale vaccination under field conditions in the tropics. the residual moisture content should be above the critical level there is always a danger that, during transportation in a tropical climate, the material will become inactivated, and inactive virus will not immunize.

The standard yellow-fever vaccine should be an aqueous base (serum-free) type. The dried product must contain not more than 1 per cent. moisture and is stored in glass ampoules sealed with nitrogen. 17 D strain of virus of 200–300th subcultures must conform to certain requirements in testing in monkeys. A safety test is performed with secondary seed virus. The serum of inoculated monkeys must show a certain standard of virulence to mice and at least five out of six inoculated monkeys must become immune. Not more than two out of six monkeys may develop encephalitis. Chick embryos from virus-inoculated eggs should not be more than 11 days old. The finished vaccine, when dehydrated to its original volume, should contain not less than 150,000 MLD as determined by the phosphoryl

pentoxide-vacuum method, and at least 500 MLD should be used to vaccinate man. Random samples must be tested on guinea-pigs, 4–5 ml. being injected intraperitoneally, and no significant clinical reaction should occur. Random samples are also tested for sterility. The labels should show date of manufacturing, date of issue, and expenditure date which should not be more than one year after date of issue. The seed virus must be preserved in the dry state under nitrogen at —70° C. If properly prepared and stored it will remain viable for an indefinite number of years. The French in Dakar use a scratch method of inoculating the yellow fever vaccine combined with vaccinia.

Other ultramicroscopic viruses resembling yellow fever.— Several of these viruses have been isolated in recent years in North and Central Africa and in South America. Their exact significance is as yet uncertain.

Durand's virus (virus D) was isolated in Tunis in 1940 and described by Findlay (1942). It is pathogenic for man as well as the guinea-pig. It is widely distributed in other laboratory animals, and in mice it circulates in the blood without any ill effects. It can be cultured on the chorio-allantoic membrane of the chick. The particles of this virus are from 38 to 57 $m\mu$ in size. Whether this virus is widely distributed as a cause of sickness in man, or whether it is mainly confined to guinea-pigs remains to be determined.

Bwamba fever (Western Province of Uganda) has been described by Smithburn, Mahaffy and Paul (1941). This disease is characterized by sudden onset, headache and backache. Symptoms subside in about five to seven days. Nine strains of filterable Bwamba Forest virus were isolated from the blood of as many patients suffering from this illness. It is pathogenic for mice by intracerebral or intranasal inoculation. Guinea-pigs and rabbits are insusceptible. The virus particles are about 113 to 150 m_u in size. Another, now generally known as West Nile virus, was found by Smithburn and Jacobs (1942) to be more widely distributed in the West Nile area, in the Bunyoro district. It is also active in the Sudan, Uganda, Kenya and in the Congo. Immune bodies to this virus have been found in the blood of forest monkeys of genera Cercocebus and Colobus. Kukuruka disease described in Nigeria is almost certainly infective hepatitis.

Mengo-encephalomyelitis virus was described by Dick and others in Uganda in 1948; it causes paralysis in man and monkeys and is related antigenically to an encephalomyocarditis virus isolated in the Pacific area. Semliki Forest virus was found in mosquitoes: it causes encephalitis in mice.

Unknown viruses capable of infecting mice when inoculated intracerebrally have been isolated from wild-caught mosquitoes. In Brazil Laemmert and Hughes isolated a virus from Aides and Psorophora, which could be transmitted by Aides egypti in the laboratory. A somewhat similar virus was isolated from Aides abnormalis by Smithburn and Haddow and is known as Uganda S. Another is known as the Bunjamwera virus, and others as Ntaya, and Zika. Altogether eight viruses have been isolated in Uganda.

All these viruses, with the exception of the West Nile virus, have been isolated from mosquitoes. Mengo virus has been isolated from Taniorhynchus africanus and T. uniformis; Zika virus from the former; Ntaya from a mixed collection; Bunyamwera from species of Aëdes; Semliki from Aëdes abnormalis and

Uganda S from A. longipalpis. There is good evidence that man becomes infected with Bwamba fever, West Nile virus and Mengo encephalomyelitis; possibly also with Ntaya, Uganda S and Zika. Mengo virus has been isolated from the blood of a mongoose, whilst the isolation of Zika, as well as the former from captive rhesus monkeys, leaves no doubt that they were naturally infected. Only in the case of Bunyamwera virus is there any direct evidence of human infection, when Southam (1951) inoculated four patients with it and produced symptoms (Dick, 1953).

CHAPTER XVIII

RIFT VALLEY FEVER

Synonym. Enzöotic hepatitis.

Definition.—An epidemic disease of sheep and cattle in Kenya, caused by a filterable virus which is transmissible under certain circumstances to man. The best account of this disease is by G. M. Findlay (1982). An outbreak in S. Africa of considerable size has been described by Mundel, Gear and others in 1951.

Ætiology.—The virus occurs in the blood and appears to be present in the plasma and attached to the blood-cells; it is found in the blood, liver, spleen, and other internal organs, but not in the urine. It may pass through the placenta of pregnant animals and infect the fœtal tissues. The size of the virus particles has been estimated by Broom and Findlay to be between 23 and 35 $m\mu$. When present in plasma, or suspended in physiological saline at pH 7.2, the virus can pass through Berkefeld N.V. and W. candles, as well as through Chamberland L_2 and L_3 candles, without any loss in virulence. Blood preserved in oxalate-carbol-glycerin has retained its virulence for mice when preserved in the ice-chest at 4° C. for eight months. Like that of yellow fever, the virus of Rift Valley fever is sensitive to the hydrogen-ion concentration of the fluid; at pH 8.0 it is destroyed. Mackenzie (1933) succeeded in cultivating the virus without loss of titre in a medium of chick embryo and Tyrode's solution. The character of this virus remains unaltered. It can also be grown on the choricallantoic membrane of the developing chick embryo.

Mackenzie and Findlay, by repeated intracerebral passage in mice which had previously received intraperitoneal injections of immune serum, succeeded in producing a neurotropic strain which causes an acute meningo-encephalomyelitis in mice but little or no necrosis of the liver. Similarly, in monkeys and lambs, a fatal encephalo-myelitis follows intracerebral injection.

Apart from the susceptibility of sheep, lambs, goats and wild game, especially buck, the pathogenicity of the virus for man and monkeys (Macaca) and many small rodents (mice, field-mice, wood-mice, hamsters, dormice, and rats) is noticeable. Mice succumb in two to four days. Cats appear to be slightly susceptible. Indian and South American monkeys of the genera Macaca, Hapale and Cebus, are relatively susceptible, but African monkeys of the genera Cercopithecus and Cercocebus are relatively insusceptible, and do not suffer from any febrile reaction. Local East African rodents have been found by Daubney and Hudson to be highly susceptible to this virus, and probably play a part in its dissemination. These are Arvicanthus abyssinicus, Mastomys coucha, and Rhabdomys pumilio.

During April and May 1944, Smithburn, Haddow and Gillet obtained the virus from mosquitoes caught in an uninhabited forest area from Mongiro, Bwamba County, in Western Uganda. The mosquitoes involved were Aëdes tarsalis and A. albocephalus, A. (Stegomyia) de-beeri subsp. de-meilloni and Eretma podites sp., containing E. chrysogaster, E. inornatus, E. ferox and E. leucopus subsp. productus. The sera of two persons from Bwamba were positive, but that of 72 wild monkeys belonging to 9 species in Bwamba were all negative. As Eretma podites mosquitoes do not occur in Kenya it is thought that the vector there is A. tarsalis and A. dendrophilus.

Using a mouse-protection test somewhat similar to that used in yellow fever, Findlay, Stefanopoulo and MacCallum have found that immune bodies can be

detected in the blood of natives from the Nuba Mountains in southern Anglo-Egyptian Sudan, northern Uganda, and French Equatorial Africa. No immune bodies were found in bloods from West Africa.

Duration of infectivity.—In susceptible animals the infection can be transmitted by subcutaneous, intraperitoneal, intratesticular, or intracerebral inoculation, by application to the scarified skin, or by instillation into the nares or conjunctival sac.

In human cases which have been tested the virus can be demonstrated in the blood for six days after the first rise of temperature, or nine days after the inoculation.

As in yellow fever, it is probable that the apparent disappearance of virus from the blood and tissues is due, not to the death of the virus itself, but to its neutralization in the presence of immune bodies.

Pathology.—The pathological change in animals consists of a focal necrosis of the liver. These foci may be discrete, as in sheep or goats, or may coalesce so as to involve the whole liver, as in young lambs, and in mice, rats and other rodents. The histological changes consist of an infiltration with mononuclear and polymorphonuclear cells, and a hyaline degeneration of the cytoplasm of the liver cells (Councilman lesions). In the livers of infected mice, acidophilic inclusions (or intranuclear bodies) have been found, by Findlay, as in many other filterable virus diseases, and similar bodies have been described by Daubney and Hudson in the livers of experimentally-infected sheep in Kenya. The nuclear changes in the affected cells are of the type known as "oxychromatic degeneration."

Symptoms.—In those cases which have been observed in man the incubation period varied from four and a half to six days. At the commencement of the fever a feeling of nausea and a sensation of fullness in the hepatic region is experienced, and this is followed by violent headaches, pain in the back, rigors, and general malaise. The face is flushed, and there is photophobia without, however, any marked conjunctival congestion. Retinal complications and loss of vision were serious and not uncommon in the S. African outbreak in 1951 and are said to be distinctive (Freed and Shrire). The tongue is thickly coated and epistaxis usually occurs. Bone pains are confined to the shoulders, back, and legs. The temperature varies between 101° and 102° F. On the fourth day of the fever the temperature falls to normal, accompanied by profuse sweating; a post-febrile weakness and a tendency to sweating on the least exertion remain. The bowels are usually constipated and the urine is deep yellow. There appears to be an initial slight leucocytosis, followed on the third and fourth days by a definite leucopenia, which persists into convalescence.

One human case has been recorded in which the fever lasted for ten days, ranging from 101°-103° F., and showed a regular saddle-back character. The virus of Rift Valley fever thus produces in man a disease resembling in many respects dengue and phlebotomus fevers. In one instance three febrile attacks of decreasing severity were noted. One fatal infection in man was recorded by Schwentker and Rivers (1934) from the Rockefeller Institute, New York. This occurred in one of the members of the staff who had been working with the virus. Although the course of the illness was otherwise typical, it was complicated by thrombo-phlebitis—a condition not previously described in association with this disease—and death was due to a pulmonary embolus. In the early stages the virus was present in the patient's blood and was pathogenic to mice. Death occurred on the forty-fifth day of the illness.

Immunity.—An immunity can be established in infected monkeys and it has been shown that they cannot be re-infected with massive doses of the virus for at least six months. In man immunity is present for at least sixteen years.

Diagnosis.—The virus of Rift Valley fever is distinguished from that of yellow fever by its pathogenicity on intraperitoneal injection for small rodents (mice and rats), and by the fact that monkeys (Macaca) immune to yellow fever are later susceptible to infection with the virus of Rift Valley fever. Human cases have also occurred in persons known to have suffered from yellow fever. The serum of recovered cases gives a specific complement-fixation reaction, and contains immune bodies which neutralize the virus when serum and virus are inoculated into mice. There is no relationship with dengue, phlebotomus fever, or West Nile virus.

Treatment.—In human cases, treatment by injection of immune serum has been attempted by Findlay, though it is not possible to estimate the result. In view of the toxic action on the liver, glucose should be given by mouth. The virus is not sensitive to sulphonamides.

Prophylaxis.—Evidently in the midst of a sheep epidemic human beings are themselves very susceptible to infection. There is some evidence to show that in the Naivasha district of Kenya, a mosquito—Mansonia fuscopennuta—may be responsible for the transmission of the virus, whilst Daubney and Hudson also report that it is possible to convey the disease by inoculation of the body-contents of other mosquitoes, such as M. versicolor and M. microannulata, though Dick has suggested that two species of Aèdes may be involved. The neurotropic virus may be of value in immunizing sheep and cattle, since on subcutaneous injection it causes almost no reaction.

CHAPTER XIX

PSITTACOSIS AND ORNITHOSIS

Definition.—Psittacosis is a disease of parrots, parrakeets and budgerigars transmissible to man. Ornithosis viruses are now known to infect a considerable number of birds, including finches, pigeons, gulls, fulmar petrels, willets (North American snipe) and ducks in Long Island and California. When the virus occurs in parrots and their relatives it is known as "psittacosis": in other birds as "ornithosis."

Epidemiology.—Outbreaks of psittacosis were at one time thought to have all arisen in Brazil, but no human cases have ever been reported in that country. There is no evidence that epizöotics of this disease occur under natural conditions amongst the parrots in the forests of Brazil, but when these Amazon parrots, especially Amazona æstiva, are in captivity, and are transported under grossly insanitary conditions to Europe, the disease arises and is able to spread.

A greater mortality from this disease occurs during the cold weather, as found by Gordon in budgerigars experimentally inoculated with psittacosis virus. The symptoms in birds are those of an acute infection. The infected bird sits listlessly, with ruffled and dirty plumage; it suffers from diarrhœa and there is usually a discharge from the eyes and nostrils. Recently, however, the problem has been further complicated by the discovery of the virus in apparently healthy birds in California and in Australia. When killed, they are found to have enlarged spleens containing the virus.

The source of infection is usually the Amazon, though grey African parrots have been the apparent cause in some of the British cases. In Australia a number of parrots caught in New South Wales have been found infected, while in the Northern Territory the Gouldian finch (Polphila gouldiæ) and the long-tail finch (P. acuticauda) carry the virus. The Bengalese finch, a hybrid between Aidemosyne malabarica and Uroloncha striata, imported from China, is also a carrier, as are the siskin and crossbill. Among the Plocidæ the Java sparrow may show infection.

Possibly canaries, blackbirds and thrushes may occasionally act as carriers, and a disease resembling psittacosis has occurred in the Faroe Islands, where apparently it is propagated by the fulmar petrel, Fulmarus glacialis (Haagen and Mauer). During the last few years an atypical pneumonia had been described from these islands. It was confined to the middle-aged and occurred in summer and early autumn. Infection appeared to be contracted by the women who pluck and salt down the fulmar fiedglings. (Rasmussen, 1938.)

The virus has been found to cause disease in pigeons in South Africa and in the United States, where at least five human cases have been reported in those who have had contact with sick birds. Pigeons have also been found infected in the Gold Coast. Andrewes and Mills (1943) isolated the virus from apparently normal pigeons in Southern England. It is not possible to tell from the appearance of the bird whether it is infected or not.

Parrots may remain in a subacute infectious condition for several years. Direct infection from man to man has been noted, and in one English outbreak the doctor in attendance contracted the disease from his patient. House epidemics, too, are apparently not uncommon, particularly in Vienna, and, according to Gerlach, human beings may act as virus carriers after imperceptible infections. Human carriers are known and one man has remained infected for eight years.

An infective pulmonary condition with a general typhoidal picture occurring in definite groups should suggest psittacosis.

Ætiology.—The virus nature of psittacosis was worked out by Bedson and Western on the budgerigar (Melopsitacus undulatus), in which the disease is highly contagious. The virus can be transmitted by citrated blood or emulsions of liver or spleen. The blood contains the virus in the early stages of the disease and as long as the tenth day. Besides parrots and parakeets, hens are susceptible. Mice are susceptible to experimental infection by intraperitoneal inoculation and, on intracerebral injection, develop encephalitis. These animals become acutely ill three or four days after injection and die of septicæmia with enlargement of the spleen.

The virus of psittacosis will pass Chamberland's L_1 , L_2 and Seitz EK filters. The size is $220-330\ m\mu$. Rabbits and guinea-pigs are susceptible to intracerebral inoculation (Rivers and Berry), as is also the Tasmanian devil (Sarcophilus harrisii). The virulence of the virus is increased by passage through mice, and an intracerebral inoculation reveals a definite neurotropic tendency (Gordon). The virus of psittacosis inoculated intratracheally or intranasally in monkeys produces a pneumonia similar to that observed in man (Rivers and Berry).

In parrots which have succumbed to a fatal dose of the virus, minute bodies are seen in the endothelial leucocytes in and near focal lesions. These Gramnegative bacillary bodies have also been found in human tissues and have been described by Levinthal, Coles, and Lillie as Rickettsia psittaci¹. The forms described in the early stages of infections of the mouse with psittacosis are developmental stages of the virus, which, according to Bedson and Bland, has a complicated life-cycle reminiscent of certain of the protozoa. These virus bodies, readily demonstrated by Giemsa's and Castañeda's stains, show considerable morphological variations. Some forms resemble bacteria: others rickettsiæ and, indeed, some authorities (Lillie) think the virus belongs to this group. Psittacosis virus, however, is best classified with the virus of lymphogranuloma venereum in a group termed by Rake the Chlamydozoaceæ.

Pathology.—The pathology of psittacosis in the parrot was described by Lillie. A fibrinous or purulent pericarditis is produced with pericardial hæmorrhages. The liver is usually enlarged and studded with white foci of necrosis with red areolæ. On microscopic section this organ showed coagulation necrosis with oxyphil, pyknotic and karyolytic liver cells. Marked proliferation of the Kupffer cells was noted, and focal infiltration by plasma cells and macrophages laden with fat.

Autopsy findings in man are those of a general septicæmia with inflammatory condition of the lungs. The spleen is normally enlarged and soft, with semi-diffluent pulp. The most striking changes are found in the lungs, which exhibit a peculiar hæmorrhagic vesicular pneumonia, complicated by pulmonary thrombosis and a mucopurulent bronchitis in which bacteria are numerous. In the microscopic pathology one of the most striking features of psittacosis-pneumonia is the variation in type of the alveolar contents, often within the same microscopic field. Some alveoli contain serum alone; some serum and red corpuscles: and some leucocytes, macrophage cells and alveolar epithelium. An interstitial cellular infiltration has been noted in about half the cases.

The lung changes were at first thought to resemble those of influenzal bronchopneumonia, but they are now recognized as a distinct type. In psittacosis the consolidation is of a lobar type with abundant fibrin formation throughout the affected areas; there is practically no polymorphonuclear reaction, and hæmorrhages occur only in relation to the more severely damaged areas. The bronchioles are involved. (In influenza the process is essentially a bronchopneumonia and the lung is nodular.) In the brain a condition known as "cerebral purpura" is not uncommon, caused by masses of red cells escaping by diapedesis from the capillaries, the walls of which remain intact.

Symptoms.—Psittacosis in man is a severe illness with a high mortality (about 20 per cent.). All ages and both sexes are affected. It is, however, as a rule, comparatively mild in young people, increasing in severity with age. In those over fifty it is usually fatal. The duration of the disease is two to three weeks. Convalescence is protracted and tedious, and may be interrupted by temporary relapses or by femoral-vein thrombosis.

During the first week the patient may feel comparatively well, in spite of high pyrexia. The fever gradually rises in a step-like fashion to attain a maximum about the end of the first week. When recovery occurs the temperature falls by lysis. The early symptoms are epistaxis and generalized pains. Towards the end of the week the whole aspect becomes more severe; the patient suffers from profound exhaustion and tends to become somnolent and intermittently irritable; there is usually a troublesome paroxysmal cough, which persists to the second week. Scattered signs of consolidation, which may eventually involve the greater part of the lung, become apparent. Constipation now becomes manifest and gives rise to tenesmus and abdominal discomfort. The nervous symptoms consist of headache, drowsiness, apathy and mental depression. During the second week a state of semi-coma with muttering delirium sets in, to such an extent that life is despaired of, but when things appear at their worst, the temperature begins to fall by lysis, and in a few days the patient gradually shows signs of improvement.

Although the illness is usually severe, yet mild and even ambulatory cases have been recorded. The incubation period appears to be about eight to ten days, but may extend to sixteen days. In man-to-man infections it is generally about four days. Pyrexia is usually of the typhoid type, and occurs in all cases; some have a gradual rise of temperature of the "step-ladder" variety.

Epistaxis is early, usually on the first, sometimes as late as the eleventh to fourteenth day. Headache is a constant feature. Chills and rigors usually occur, and with the latter a temperature of 104° F. has been noted. Generalized influenza-like pains are the rule. The throat is usually sore and congested, and in a few cases the tongue is swollen and sore, in the condition known as "peribuccal cedema." The lungs are involved in almost every case, with a cough of varying intensity, but the sputum is scanty; it may be rusty, characteristic of lobar pneumonia. The physical signs in the lungs vary considerably. A relative bradycardia is the characteristic feature of the cardiovascular system. With a temperature of 103° F. the pulse is about 90 and this feature increases the typhoidal-like character of the disease and, indeed, the typhoid state accompanies all severe cases. Photophobia is also a feature, and, towards the end of the first week, most patients become lethargic, with stuporose appearance, sluggish speech, and blunted mentality.

"Rose spots," or similar skin lesions, have been noted in nine British cases, at varying periods from about the seventh to the thirteenth days. The spots were on the chest and abdomen, more rarely on the back, measured 2–4 mm. in diameter, and faded on pressure. Parotitis has been noted twice. The blood picture in characteristic psittacosis is not markedly altered. Ambulatory cases may have a fatal relapse.

Diagnosis.—On clinical grounds the diagnosis of psittacosis is not easy, as it has many features in common with typhoid. The gastro-intestinal symptoms may resemble those of that disease, but perforation and hæmorrhage never occur. The spleen is usually palpable in typhoid, but in only two out of 80

cases of psittacosis has this been recorded. With influenza, too, it has many features in common. Blood-cultures and agglutination reactions are completely negative in psittacosis, and inoculations of blood or sputum in the early stages of the illness will prove fatal to mice. Apart from isolation of the virus, the most satisfactory method of diagnosis is by the complement-fixation reaction. According to Bedson, the most satisfactory antigen is obtained from the spleens of infected mice, as it is essential to employ material that is rich in it. Antigen may also be prepared from cultures of the virus on agar-serum or chick-embryo medium. The technique is similar to that of the Wassermann reaction. It is diagnostic 8–12 days from the beginning of the disease, when it occurs 1 in 2–1 in 8 and in higher dilutions. There is a non-specific fixation with syphilitic sera up to 1 in 8.

Differential diagnosis.—Psittacosis in parrots has to be differentiated from Pacheco's parrot disease, which was discovered by Pacheco, Bier and Meyer, while investigating pathological conditions of parrots in Brazil. The filterable virus produces a clinical picture similar to psittacosis, but it differs from psittacosis virus in not being communicable to man or pathogenic to mice, while in the necrotic liver cells there are large acidophilic intranuclear inclusions.

Prognosis.—The mortality rate in human cases so far reported is high—usually about 20 per cent.—and convalescence is slow and tedious.

Treatment.—Symptomatic treatment and nursing should be on similar lines to those of typhoid. The majority of strains are sensitive to penicillin which should be given in doses of at least 400,000 units a day. Some strains of ornithosis virus are also sensitive. *Chloromycetin* is specific for the psittacosis virus (Smadel). Serious cases have been treated with *aureomycin*, 500 mgm. by mouth, every four hours. The results are dramatic (Hamke, 1951).

Prophylaxis.—The best method of avoiding a disease which is conveyed by birds of the parrot family is to avoid contact with these birds. Petting parrots, and especially insertion of the beak into the mouth, should never be allowed. The importation of members of the parrot family and finches into countries where the disease is not endemic should be prohibited. Care must be exercised by those capturing nestling sea birds, especially fulmar petrels—a practice which is now prohibited in the Faroes.

CHAPTER XX

RABIES

Synonyms. Hydrophobia; Rage (French); Tollwut (German); Lyssa; Rabbia (Italian).

Definition.—Rabies is a disorder of dogs and other animals. Under natural conditions it is transmitted both to animals and man by inoculation of virulent saliva in the act of biting.

It is now realized that it is caused by a virus, which invades the central nervous system by the peripheral nerves, and becomes fixed there. The incubation period is in some cases very long, and the centres for respiration and deglutition in the brain are severely attacked, so that spasm and, eventually, paralysis result. Protection is afforded by inoculation with attenuated or killed rabies virus and, to some extent, by antirabic serum.

Geographical distribution.—There is no part of the earth where man and other terrestrial animals can live where rabies cannot potentially exist. It occurs quite commonly in Greenland, Iceland and other Arctic countries, but it is possible that in the Far North a special modified form exists. In the tropics and subtropics, especially where jackals, wolves, foxes and wild dogs abound, a specially virulent form is sometimes prevalent. In South America and in the West Indies, cattle are commonly affected 1, constituting a reservoir of the virus, and in Jamaica the vampire bat plays an important part in dissemination. Australia is said to be free from this disease, and this freedom is ascribed to the peculiar fauna and the rigid quarantine which has been imposed upon dogs.

Rabies has been stamped out from Great Britain for nearly fifty years, except for small outbreaks among dogs when an animal has been smuggled into the country by aeroplane. It is very prevalent indeed in India, where, on account of the numerous and dangerous bites from wolves and jackals, it causes a high mortality. Statistics are difficult to obtain, but an average of about 5,000 persons are treated annually at the Pasteur Institute, Kasauli.

In the United States of America 10 states or territories are considered to be free from the disease, both in man and animals, and until recently it accounted for about 100 deaths a year.

Animals susceptible to rabies.—All warm-blooded animals are susceptible, under favourable conditions, to experimental inoculation of the rabies virus; it is more commonly met in nature in those mammals which are subjected most often to the bites of dogs, wolves and foxes. Some species are rarely infected, either because they are seldom subjected to bites, or because they are provided with thick fur.

There is some reason to believe that skunks, weasels, stoats, civet-cats, and possibly the meerkat (Cynictis penicillata) may propagate the disease widely among their own kind, as does the dog. The susceptibility of rats to subcutaneous inoculation led to the opinion that these animals might also be capable of perpetuating this disease in nature, but of this there is little evidence. Therefore, in South Africa meerkats act as a reservoir, while in the United States grey squirrels may play a similar rôle.

Domesticated animals are affected with the following percentage frequency: dogs 85·1; cattle 10·7; horses 1·48; swine 1·12; cats 0·81; sheep 0·7; goats 0·09. Donkeys are rarely affected.

¹ In South America rabies in cattle is—perhaps wrongly—termed "Mal de Caderas."

Wolves, foxes and rabbits may be affected in countries where they abound. Birds are relatively insusceptible to inoculation and this is said to be due to their high body temperature. Frogs are said to be susceptible.

The alleged disproportionate prevalence of rabies during certain seasons of the year appears to have little foundation in fact. In India one-third of the cases are inflicted by jackals, 50 per cent. of mad dogs excrete the virus in the saliva, whilst rabies following scratches is rare.

Ætiology.—The symptoms of rabies indubitably point to an intoxication of the nervous system, while the pathological changes also indicate that this is the part affected.

The most generally accepted view of the infection is that the virus of rabies, upon its introduction beneath the epidermis, finds its most favourable medium for propagation in nerve-endings and fibres torn in the region of the bite. Along the course of the axis cylinders it develops and travels, without disturbing their function, until the central nervous system is reached. The virus is strictly neurotropic (septinévrite), although Marinesco and Stroesco consider that the main path of dissemination is by the lymphatics. Finally, the cells of the central nervous system are attacked, the first effect being excessive stimulation, followed by destruction. At the same time a neurotoxin is produced which is responsible for some of the symptoms. Nerves leading from the site of the inoculation to the central nervous system have been shown to become progressively infectious in ascending segments, while complete section previous to inoculation confines the toxin to the lower segment. The blood and lymph appear to be incapable of taking up the toxin from the site of inoculation.

Street virus ("virus des rues," "Strassenvirus") is the strain found in the virulent nervous tissue infected by the natural disease¹; its virulence is very variable and, when inoculated subdurally into rabbits, it causes symptoms of rabies after a variable period of more than fourteen days. Inoculations should, if possible, be carried on for several passages, till the nature of the virus becomes clear. Considerable variation in street virus occurs, some strains showing rapid adaptation to the central nervous system. Certain strains from wolves are known as renforcé and produce paralysis in rabbits after a short

incubation period.

Fixed virus (virus fixe) is modified from the street virus by passing through a long series of rabbits. In this manner its virulence becomes greater for these animals, so that finally they develop the disease after a constant or "fixed" period of inoculation, after which no further pussages can reduce the incubation period below this span. This virus does not normally produce Negri bodies. The mouse, however, appears to be the most suitable animal for rapid diagnosis.

Nicolau and Kopciowska were able to pass a strain of rabies virus from sciatic nerve to sciatic nerve for more than one year, and have thereby reconverted "fixed virus" into "street virus." The strain of fixed virus has been passaged in the laboratory for six years and gives rise to from one to four Negri bodies in 100 ganglion cells of the horn of Ammon. This transformation was achieved by passage inoculations made into the right sciatic nerve, the emulsions employed being obtained from the *left* sciatic nerve of the previous animal. With great trouble, two lines of passage have been obtained covering a period of more than a year.

Negri "bodies."—Negri originally described certain oxyphilic granules in the nerve-ganglia cells of the hippocampus major. Although they are probably of the same nature as the cytoplasmic inclusion bodies found in association with

¹ The disease known as *Oulou-futo* among the natives in West Africa has been shown to be identical with rables. Nicolau, Mathis, and Constantinesco claimed that this virus is less virulent, and more difficult to fix, than the true rables virus.

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other ultramicroscopic viruses, yet Negri bodies are admittedly very constant in rabies, peculiar to it, and useful for diagnosis.

Covell and Danks, after micro-incineration and other studies, concluded that the Negri bodies arise from constituents in the nerve-cell as a result of the virus. They are not present in every case of rabies, but when a person has been bitten by an animal having symptoms suspicious of rabies, preventive treatment should at once be instituted. Inoculation tests have shown that this practice is sound. The custom of killing suspected animals immediately after they have bitten their victim is not recommended, as this practice operates against the demonstration of Negri bodies which may be present in the later stages of the disease. Furthermore they have to be distinguished from the Lentz bodies! Other changes in the nervous tissue, of less importance from a diagnostic view, have been described, and Courmont and Lesieur claimed that in the dog there is a relative polymorphonuclear-leucocyte increase in the blood and in the lungs; whereas in the normal dog these cells average 53 per cent., in the rabid animal they form 90 per cent.

Passage of virus in carnivorous animals.—When passed through dogs the virus does not lose its potency; on the contrary, it becomes fixed with an incubation period of eight or nine days, but in rats street virus becomes rapidly augmented in virulence; on the other hand attenuation and, finally, loss of virulence is produced when monkeys, frogs and birds are inoculated.

Location of the virus in the body.—The central nervous system and the peripheral nerves contain the virus with constancy, but infectiousness is variable in different parts of the nervous system. It was found by Nitsch that 01 mgm, of the brain cortex (fixed virus) was lethal to rabbits in seven to nine days, whilst 0.5 mg. from the centre of the cord was not virulent, though 1.0 mgm. was. The medulla, for instance, is five times more virulent than the rest of the cord. The salivary glands of dogs are constantly infectious. The generally accepted view is that the virus finds its way to these glands by way of the nerves and, according to Remlinger, the saliva of a dog may remain virulent five days after apparent recovery from rabies. In man the salivary glands are seldom invaded. The blood is non-infectious, either in man or in experimental animals. There is no evidence that the virus can be conveyed to the foctus. Neither the milk, urine, liver and spleen, nor spermatic fluids ever harbour it.

Cultivation of the virus.—Although there is considerable doubt whether the virus can be successfully grown in the choric-allantoic membrane of the developing chick embryo, it has been grown successfully, either in a plasma medium or in serum-Tyrode, containing mouse- or chick-embryo tissue. Human and simian are more satisfactory than rabbit serum for this purpose. The causal agent of rabies is a virulent substance of a protein nature. Endowed with powers of assimilation it can be cultured on the choric-allantoic membrane of the chick embryo. Rabies virus occurs, not only in the nervous system and salivary glands, but also in almost every organ. It has been demonstrated in the suprarenals, spleen, liver, kidney, lung, testicles, retina, choroid, vitreous, crystalline lens, but not in the aqueous humour.

The Swiss mouse and white mouse are the animals of choice for experimental work; the former is ten times more susceptible for rabies virus than the rabbit or guinea-pig and is incomparable for assessment for the immunizing power of different antirabies vaccines.

Desiccation does not attenuate, but preserves the rabies virus. Now in almost every country the classical method of Pasteur and dilution method of Höegyes have

¹ Lentz bodies occur in the sympathetic ganglia and extracellularly between ganglion cells of rabbits injected with fixed virus,

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been replaced by the use of etherized or phenolized vaccines which retain their immunizing properties for months and can be despatched far and wide. Paralytic accidents complicating antirabic treatment are on the increase. It is important to distinguish between "rage de laboratorie," where the virus used in treatment is recovered at autopsy, and the "paralytic accidents," whilst usually less serious, are much more frequent. In most countries cattle, horses, sheep, pigs and goats are being successfully immunized after having been bitten by rabid animals.

Powell and Culbertson have succeeded in cultivating fixed rabies virus in embryonated duck's eggs. The eggs were infected intra-amniotically and growths harvested after 14 days. Apart from the embryo itself a degree of infectivity could also be detected in the extra-embryonic fluids. The strains have been carried on for three generations and seem to have lost some of their virulence for mice, and when used as a vaccine this material protected against 700 L.D. as determined by the mouse potency test.

Properties of the virus.—The particle size of the virus of fixed rabies is $100-150~m\mu$, as determined by filtration. Centrifugalization renders the supernatant fluid of an emulsion avirulent. The virus is sensitive to heat; thus ordinary undried emulsions lose virulence after exposure to 50° C. for sixty minutes and to 60° C. for thirty minutes. In the dried form, however, the virus resists 105° C. for two minutes. On the other hand it can withstand intense cold (liquid air at —190° C.) for three months, and 50 per cent. glycerin for many months.

Desiccation.—Rapid desiccation of brain and spinal cord is not destructive to virulence, and virus in this state can be preserved in stoppered bottles in the dark for nine months. Gradual desiccation at higher temperatures (23° C.) is accompanied by gradual attenuation, so that virulence is usually lost in five or six days.

Filtration.—Emulsified rabies virus passes through the pores of Berkefeld filters, but not finer than L_3 in the series of Chamberland bougies, and it is claimed that fixed virus passes through finer pores than street virus.

Chemical agents.—Rabies virus is sensitive to the action of acids and alkalis, but more resistant to chemical disinfectants than are bacterial emulsions. Probably, when it is introduced into the subcutaneous tissues, leucocytes and other cells are capable of absorbing it. The serum which is immunized against rabies is able to destroy the activity of the rabies virus in vitro. From immunized sheep a serum of a very high antitoxic titre has been obtained.

The Trinidad disease (Paralyssa).—Hurst and Pawan (1930) described a curious paralytic form of rabies in Trinidad. It appears to affect, and be spread by, the vampire bat, which in South America and in the Antilles feeds indiscriminately on the blood of man and cattle. Oviedo in the 16th century described the death of forty Spaniards from the bites of vampire bats. disease was first noticed in cows; subsequently five cases were discovered in man, and the virus was transmitted to monkeys. This disease is apparently identical with "mal de caderas" of South American cattle, but is probably better termed South American lyssa. Some doubt has been expressed whether the bat at first identified by Pawan was the vampire or a harmless species of the genus Artibæus, but Lima (1934) in Brazil by direct experiment, brought forward evidence that, in the State of Santa Catherina, epizootics of paralyssa are prevalent in the favourite haunts of vampire bats (Desmodidæ) and that the transmitter is the local species (Desmodus rotundus). The virus may be demonstrated in their saliva and they act as carriers for considerable periods. Kraus and Duren suggested the designation "Paralyssa" for this form.

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Incubation period of rabies.—This is remarkable for its length and great variability. In nature it is seldom under ten days, but may extend to a year, or even to three, though in the majority of cases the disease develops before the end of the third month.

The length of the incubation period is influenced by the following factors.

(i) The species of animal: it is usually longer in man than in the lower animals.

(ii) The site of the inoculation: the shorter the distance from the brain, the shorter will be the period of latency, whilst females exhibit a shorter period than males, and children than adults. (iii) The severity of the wound and the physical condition of the patient have an undoubted influence.

Webster gives the incubation periods as :-

Bites on head, face and neck . . . 30 days.
,, upper extremity 40 ;,
, lower extremity 60 ,,

Symptoms and clinical course.—Rabies presents two distinct clinical types: the furious or excited, and the quiet, "dumb" or paralytic. Some distinguish four types of the disease: cerebral, medullary, cerebellar and sympathetic.

The excited or furious type.—The onset of rabies is usually rapid; the patient shows some psychical change very early, becoming anxious, melancholy, and possessed of strange presentiments. Sleep becomes impossible. Soon, local numbness, twitching, and a sense of itching progress from the wound, which becomes engorged and tender. Sometimes the first symptom is a strange sensation in the throat or a sense of constriction of the fauces.

The mental symptoms may be purely hysterical, and many cases have been recorded in which the onset is determined by mental shock, though fright and terror may be regarded as manifestations of the disease. An initial rise of temperature is perhaps the most constant early sign.

Symptoms may last several days before the outbreak, but usually only twenty-four to forty-eight hours. Hydrophobia, the outstanding symptom, prevails in the great majority, and arises from extremely painful spasms of the organs of deglutition and respiration induced by attempts to eat and, especially, to drink. These spasms are so agonizing that they exceed, possibly, all other forms of human suffering; the sight or smell, or even the sound of liquids, is sufficient to excite an attack. When an effort is made to gulp down a small quantity of liquid it is expelled, with an anguishing spasm of the throat and larynx. This condition is a state of hyper-susceptibility of the nerve-cells to external stimuli. Draughts of air may bring on a convulsive seizure; skin and tendon reflexes are exaggerated; respiratory spasms involve the thoracic muscles and cannot be relieved by intubation. Solid foods are usually more readily taken than fluids.

The disease progresses rapidly. In the majority of instances there may be periods of latency which cause hope of recovery and doubts of the diagnosis. The mind is usually exceptionally clear, questions being answered with intelligence until the voice becomes indistinct and words unintelligible. But there are periods of excitement which may be truly maniacal; the patient may injure or destroy any objects near at hand, but there is seldom any tendency to injure other persons. Sexual excitement, accompanied by priapism, is frequent. The voice usually becomes hoarse; the strange sounds emitted during expectoration at the onset of the seizure have given rise to the popular conception of "barking like a dog."

The convulsive seizures become more and more pronounced until paralysis leads to death. The muscles, which have been racked to the limit of endurance, become limp, and the face, previously expressive of terror and suffering, becomes expressionless. There is usually an excessive secretion of ropy saliva, which the patient is unable to expel. Finally, the breathing becomes irregular and feeble

and at last ceases altogether. The temperature rises before death. Sugar and acetone are usually found in the urine. In the paralytic stage the pupil is dilated.

The paralytic type in man.—Because symptoms are less marked than in the violent type, this undoubtedly remains unrecognized in many cases. For a time the mere existence of this form was forgotten. Pathologically it has been attributed to infection with a large amount of virus and to the involvement of the spinal cord rather than the brain. The onset takes place with high fever, general malaise, headache, and vomiting; afterwards there is localized pain, especially in the bitten parts; a heaviness and numbness of these regions follow, then ataxia, weakness, and finally paralysis. Girdle sensation is usually present.

Consciousness is retained until late in the disease. Paralysis spreads, with preceding or accompanying pain in the affected parts, involving limbs, trunk, rectum, bladder, face, tongue, and eye muscles. Some difficulty in swallowing liquids results from the respiratory embarrassment, but "hydrophobia" is usually absent. Frequently, normal respiration may be temporarily restored and death takes place from cardiac paralysis. This form of the disease is more prolonged than the furious type, lasting up to seven and a half days, as compared to the average duration of three to four days in the latter.

Rabies in the lower animals.—On account of its highly developed intelligence the dog shows the most marked psychical disturbances, and when it begins to exhibit marked and causeless changes in disposition, suspicion of rabies should be entertained, especially if there are other reasons. The dog may become more morose, sullen, or irritable, or show excessive affection. Fatal infections are apt to occur at this stage through licking wounds or abraded surfaces.

A very characteristic symptom is the change in the character of the voice, which is said to resemble the yelping of a tired foxhound giving tongue. The rabid dog is easily startled, growls or barks on the slightest provocation, and may bite other animals, or man; he bites them, or passes by, but never swerves to attack them.

The popular idea of a rabid dog as an aggressively mad animal is incorrect. On the contrary, it looks ill, takes no interest in its surroundings, trots along with a wavering gait, often with unilateral drooping of the ear. Convulsions soon appear and the animal may die during one. More frequently, a paralytic stage supervenes and the dog drags itself to a secluded spot. In contradistinction to its usual habit, it swallows sticks and stones and other objects. Swallowing, at first difficult, later becomes impossible.

The paralytic form is most frequent amongst dogs, and is peculiarly dangerous to man. The dog becomes the object of sympathy so that bystanders often become scratched or bitten. Such rabid dogs are intensely thirsty and have no fear of water but, owing to the paralytic condition of the throat, they are unable to swallow. Glycosuria is a common symptom of rabies in animals, and is said not to be of renal origin.

The paralytic form is very common in herbivora, but horses present the most agonizing type of the furious form.

Experimental rabies in the rabbit.—After subdural inoculation, rabies manifests itself by a premonitory fever; the animal appears sleepy and does not eat. The appearance of the face is characteristic, the eyes have a staring expression and frequently there is drooping and lopping of one ear. The animal urinates more frequently than normal. Rarely, the furious stage supervenes, convulsive seizures are frequently observed and there is grinding of the teeth. Paralysis begins in the hind legs and proceeds forwards. Abortion is common in pregnant females.

Mortality in untreated and treated persons.—Once rabic symptoms develop the disease is invariably fatal and the average mortality varies from 5-15 per cent.

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It is highest from wolf-bites, more especially on head and face and higher in deep than in superficial wounds. Remlinger considers that of 1,000 persons treated in an antirabic institute for dog-bite probably only 500 have been bitten by rabid dogs as the death rate in such persons would be about 15 per cent. We may expect 75 out of the 1,000 would die of rabies, if untreated. The mortality in treated persons is about 5 per 1,000 and it appears that antirabic treatment saves 70 per thousand so treated. The mortality from untreated wolf-bite is 60 per cent., and it is rare for these animals to bite unless they are rabid; yet the mortality in cases of wolf-bite which have been subjected to treatment is not more than 15 per cent. (Remlinger). It is therefore justifiable to continue to regard antirabic treatment as of some value in the prevention of rabies, though it may not act by the orthodox method of active immunization.

Immunity.—Natural immunity to rabies is exhibited by a number of lower vertebrates; occasionally in mammals an *individual immunity* may be observed, and a state of *hereditary immunity* has been, somewhat doubtfully, described by Remlinger and Konradi.

Much more is known about acquired immunity. Man and animals may be rendered immune by inoculation with modified virus of rabies; secondly, their blood acquires "rabicidal" properties, that is, the power to render inert the virulent material exposed to its action in vitro.

Immunity to rables can be conferred by increasing doses of filtered emulsions, especially those exposed to high temperatures.

Levaditi and Stoel showed that the virus of rabies is maintained, and probably multiplies, when placed *in vitro* in contact with cellular elements. The virus develops in contact with embryonic cerebral tissue *in vitro*.

The virus is more virulent in rabbits, inasmuch as it causes the disease more rapidly, but at the same time it loses virulence for animals higher in the taxonomical scale. It is assumed that, by passage through rabbits, the virus becomes augmented, hence the early onset and the paralytic symptoms. Its resistance to the inimical action of the body juices is thought to be reduced; hence the harmlessness of subcutaneous injection. The argument in favour of the toxin of rabies being an ultramicroscopic virus is the production of symptoms of fever, emaciation, and cachexia after passage through a filter. Glusman, Solonjowa and Predtetschenkaya have found that the virus can pass through Chamberland bougies L_2 and L_3 . Occasionally during inoculations, or soon after, paralytic symptoms appear, apparently not directly due to rabic infection. Paralysis of the Landry type is often noted. These paralytic accidents, which are associated with demyelinization in the nerve sheaths, are probably of an allergic nature.

There are other peculiarities of the rabies virus toxin; thus, the spinal cord of the rabbit, when dried until it has lost its infectiousness, has also entirely lost its immunizing properties. It is therefore possible to explain artificial immunity conferred by injection of fixed virus. The successive injection of dilutions of fixed virus, increasing from weak to strong, or of emulsion of the dried cord has the following effect: the rabies toxin contained within them arrives earlier at the cells of the central nervous system by way of the blood and lymph circulation than it does by progressing along the nerves, so that when it arrives at the centres, the protoplasm of the cells has already become accustomed to the action of the rabies toxin; consequently the virus, introduced during preventive inoculation, can no longer affect them and produce chromolytic changes. Unattenuated "fixed" virus may now be used for production of immunity, for there is no danger of producing rabic infection from its subcutaneous injection. It has recently been shown that, in the presence of a pointolite, rabies virus may be inactivated by the photodynamic action of dyes, such as methylene blue or proflavine, in high dilutions. Inactivated virus, however, retains its antigenic power.

Diagnosis and differential diagnosis.—The diagnosis of rabies rests upon the consideration of many factors, such as the history of exposure to infection, the length of the period of incubation, the clinical symptoms and course, the termination, and the post-mortem findings, confirmed by inoculation tests on animals.

In recounting the history of exposure to the virus, due consideration must be given to the mental excitement of the patient and to the fact that the rabies may be infectious several days before the appearance of rabid symptoms in infected animals.

Very often it happens that no history of infection may be obtained until late in the disease, or until after death. There are instances where the victim has died of rabies, yet the infecting dog has recovered. In assessing the length of the period of incubation, well-authenticated cases of rabies may commence as early as ten days after exposure, but hysterical manifestations come on a few hours or days after assumed exposure. The mental behaviour of the patient during the probationary period may assist in diagnosis, but many cases show no disturbance whatever until tell-tale signs develop. The chief difficulty is, of course, with hysterical manifestations, and it is stated that hypersensitiveness to draughts of air, common in true rabies, is not evoked in hysteria, so that fanning a patient may produce a convulsive seizure. Tetanus and mania may also simulate rabies. The absence of trismus in one, and of convulsive seizure in the other, will help. Some paralytic cases of rabies may resemble Landry's paralysis.

In the lower animals there is a variety of diseases, such as dog distemper, dog hysteria, or brain tumour, which may simulate rabies. The hysteria of dog distemper and true dog hysteria have to be differentiated. Then there is the pseudo-rabies or "mad itch" of Aujeszky. This virus is much more resistant to desiccation. Remlinger and Bailly found that the intraocular route is the most practical method of differentiation in experimental infections, because in pseudo-rabies the issue develops suddenly, which is not the case in true rabies. The infection is transmitted along the axis cylinders of the nerves, reaching the ganglia and segments of the cord, producing this degeneration which is probably responsible for the itching from which the disease takes its name. Pseudo-rabies has occasionally occurred in men, as a result of handling infected animals. It is a non-fatal disease and is characterized by intense itching.

Cases of "psychological" rabies have occurred in medical men and veterinarians bitten by dogs suspected of having rabies. Apart from psychological symptoms, there are no nervous changes.

TREATMENT

Indications for treatment are:—If the biting animal is clinically rabid, especially when confirmed by laboratory tests, in endemic areas after the bite of a stray animal or dog, or after handling an animal diagnosed as rabid, when there are fresh abrasions of the skin contaminated by saliva.

(a) Treatment of the developed disease.—No cure has yet been devised for the fully developed disease. As in other virus diseases, a potent antirabic serum has no effect once the symptoms have begun. Therefore, fully developed rabies in man must be treated on symptomatic grounds. Chloroform inhalations are given for control of painful spasms; chloral and bromides per rectum and, if possible, curare, subcutaneously. Morphia is apt to increase the mental excitement and suffering. Where the patient cannot swallow food, rectal alimentation is to be preferred to feeding by stomach-tube. Intubation or tracheotomy are probably both useless for the relief of dyspnæa and suffocation. Mechanical restraint is generally unnecessary and should not be resorted to except in violent maniacal forms. The attendants must preserve a calm and pleasant demeanour

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and, when speaking of the disease, should do all possible to reassure the patient. Penicillin and the sulphonamides are useless.

- (b) Prophylactic treatment of person exposed to infection.—Cauterization of the infected wound has been practised since time immemorial and, when properly carried out, it is undoubtedly of some benefit. It has been shown by experiment that the incubation period is prolonged, even when it does not prevent extension of the infection, and thus permits more time for establishment of immunity by antirabic inoculations. Actual cautery is very painful, and is efficient only if done thoroughly and instantaneously. Experimental work on guinea-pigs shows that application of iodine, or washing with soap and water is as effective as cauterization.
- (c) Preventive inoculation.—The Pasteur treatment for the prevention of rabies in exposed persons is designed to confer immunity during the period of incubation. The production of this immunity is necessarily a long process, but, fortunately for humanity, the incubation period of rabies is normally much longer. In persons in whom, from a combination of factors, the incubation period is very short, the Pasteur treatment fails.

The principle upon which the Pasteur treatment is based may possibly rest upon the production of immunity by inoculation of modified rabies virus. However, it is much more probable that the value of antirabies inoculation depends on the interference phenomenon where the killed or attenuated virus particles prevent the virulent particles from reaching susceptible nerve cells. This has been finally accomplished by serial passage of the virus through rabbits until a fixed degree of virulence has been reached, and secondly, by its attenuation by desiccation. The first of these processes is the more important and the one most frequently employed at the present time. The following methods have been employed:

Laboratories producing antirabic vaccine must periodically test the properties of the strain, by neutralization tests with antiserum samples in mice. Mice must be immunized with vaccine ready for use by intracerebral injection. In such tests it is customary to inject the subsequent or "challenge" dose of live virus by a rate which kills all control animals.

The mouse immunity test vaccine to be assayed is diluted $\frac{1}{10}$. Thirty-two week-old mice are required. Canine vaccine is given intraperitoneally to each of sixteen. For vaccines for human use mice are given 3-6 injections. Three weeks after the first injection of vaccine sixteen control mice are divided into four lots and injected intracerebrally with $1:10,\ 1:100,\$ and $1:1,000\$ (40-50) doses. Both test and the sixteen control mice are examined for 60 days. Vaccine effective for mice is equally effective for dogs. Phenolized vaccines, however, fail to immunize mice against a subsequent intracerebral challenge. It is difficult to protect laboratory animals by antirabic treatment after injection.

- (1) Unmodified fixed virus, introduced by Ferran: 0.08 grm. of cord of a rabbit dead of a fixed-virus infection is emulsified with the aid of fine sand, using 8 ml. of salt solution or bouillon: 6 ml. of the supernatant fluid is injected subcutaneously into three different parts of the body, 2 ml. in each. The injections are repeated on five successive days.
- (2) The dilution of fresh-fixed virus, a method introduced by Höegyes, who maintained that attenuation could be more accurately controlled by diluting the fresh virus with salt solution and increasing the dosage, as treatment progressed, by increasing the strength of the emulsion. An improvement suggested by Harvey and McKendrick is to take smaller amounts of an original emulsion of fixed virus prepared from the spinal cord of a rabbit dead of a fixed-virus infection, rubbing it up with sterile salt solution in the proportions of 1 in 100.

Dilutions are prepared varying from 1 in 200 to 1 in 10,000. The dilutions are then used for immunizing. For severe cases, such as head or face wounds, as many as five injections are given daily in dilutions varying from 1 in 2,000 to 1 in 10,000, in the first four days, and subsequently, to the twentieth day, two or three times daily. Formulæ have to be devised to suit individual cases.

- (3) Fixed virus attenuated by drying.—The original method of Pasteur, and one still most extensively practised, has the advantage that it may be administered by private practitioners at some distance from the laboratory, since dried virus can be preserved by glycerinization, and despatched in this condition. The original scheme of Pasteur has been greatly modified, according to the time consumed by the treatment, by dispensing with some of the more attenuated cords, and by increasing or diminishing the dosage at individual injections. In the first four days two 3 ml. injections are made daily of emulsions of cord dried in vacuo 14, 13, 12, 11, 10, 9, 8, 7 days respectively. The total course of treatment is twenty-one days.
- (4) Fixed virus attenuated by heat.—A method advocated by Babes appears to be merely a more difficult method of attaining the same result as by the desiccation method.
- (5) Fixed virus acted on by glycerin.—While glycerin possesses the power of conserving rabies virus in an active state for a month or more, on prolonged exposure this virulence is lost, although the immunizing power may be retained. This is the method which was advocated by Calmette, although rarely is this immunity sufficiently substantial to withstand subdermal inoculation tests with the fixed virus.
- (6) Marie claimed that a rapid immunity is secured by treating a fixed virus partially neutralized by antirabic serum in vitro. It is said that a virus of high immunizing power, but of diminished infectious properties, can be administered. For this method one gramme of the medulla of rabbit is taken. A passage-fixed virus is rubbed up with 9 ml. of veal broth and the emulsion strained through cloth. To 2 ml. of this emulsion is added 4 ml. of antirabic sheep serum, previously heated for thirty minutes at 56° C. The 6 ml. of mixture is injected into the skin of the abdomen in two places and the same injections are repeated on three following days.

Formalinized virus which has been grown in tissue-culture can confer considerable immunity to mice, while after exposure to ultra-violet light it is still antigenic.

(7) The carbolized fixed virus is used at Kasauli and other stations in India. The whole brain is removed and a solution containing 1 per cent. of phenol in 0.85 per cent. salt solution is mixed and placed in a mortar in an incubator at 37° C. for twenty-four hours—sufficient to kill the virus. The suspension is stored at O° C. while tests are being carried out, and is used as a vaccine after two to three weeks' storage.

Before inoculation the suspension is again diluted with an equal part of 0-85 per cent. salt solution, so that it finally contains 0-5 per cent. brain substance. Each patient, however severely bitten, receives 4 ml. of this suspension daily for a period of fourteen days.

In India those at risk receive 2 ml. daily for seven days; those most at risk 10 ml. for 14 days. The antirabic treatment fails in severe wounds of head and face. McKendrick gives the overall mortality in treated persons as 0.33 per cent., in Europeans as 0.15 per cent., and in non-Europeans as 0.56 per cent.

(8) Chemical vaccines, phenol, chloroform and formol inactivate the virus, if left in contact for a sufficient time. There is some evidence that chloroform vaccines are the better immunizing agents. Attenuation by ultra-violet light has been extended to brain tissue and such vaccines are considered the most

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potent. In this respect it is found that the Pasteur strain is a more efficient antigen than virus fixe preparations from Indian strains.

Serum therapy.—Although, when it was first discovered that rabies serum was capable of destroying rabies virus in vitro, hopes were entertained of its

beneficent action in man, results have been disappointing.

The indications for the Pasteur treatment.—All persons who have been bitten by rabid animals, or who have had open wounds or scratches contaminated with the saliva of rabid animals, should receive the treatment. If, however, the suspected animal remains alive and well for ten days after the bite, treatment may safely be discontinued. In persons who have drunk the milk of infected cows, the possibility of infection is very remote, as gastric juice destroys the virus. Everyone who has been bitten by animals presenting symptoms of rabies should receive antirabic treatment, whether or not the suspicion is confirmed by histological examination, and pending the result of inoculation tests. Those persons who are bitten by animals which do not show any of the symptoms of rabies should not be exempt from the necessity for treatment until the biting animal, which should be carefully confined and watched, is shown to be free from the disease. It must be emphasized that histological examination is conclusive only when Negri bodies are demonstrable in the central nervous system.

The results of the Pasteur treatment.—Even with the most careful assessment of the results of treatment, it is extremely difficult to determine exactly the mortality-rate after the bite of a rabid dog. In untreated persons the estimated mortality is about 14.8 per cent. in 122 persons (Doebert, 1909). In 1935, 118,000 people received prophylactic inoculation. Figures published by the League of Nations show that from 1929-1935 only 0.4 per cent. of 524,258 people receiving antirabic treatment died from rabies. Though many were not bitten by rabid animals, nevertheless the impression remained that mortality would have been greater if they had not been so treated. As a general statement, it may be said that the total mortality of bitten persons subjected to antirabic inoculations is about 1 per cent., of whom half could not, on account of the short time permitted for the establishment of immunity, have been expected to live. Comparison of statistics from various Institutes giving antirabic immunization does not show any marked preponderance in favour of any particular method as there are so many variables to be taken into consideration, such as the situation of the bites, the interval between bite and the initiation of treatment, the thoroughness with which rabies was diagnosed in the biting animal and the length of time during which the patient was followed up after the end of treatment.

There is growing evidence that the Pasteur treatment is not a true immunization but is the result of immunization.

Myelitis following antirabic vaccine is a rare complication. Tranverse myelitis, which may be transient, has been recorded. Russell (1946) has described a case in which myelitis terminated in bulbar palsy; virus or toxin was held responsible. This presupposes that the heterologous brain substance in the vaccine is toxic to the central nervous system. This may be directly cytotoxic or anaphylactic, the patient becoming sensitized by repeated injections. These cases of demyelinating disease are essentially similar to the demyelinating encephalomyelitis associated with vaccination.

Polyneuritis.—The Gullian-Barré syndrome consists of polyneuritis, with frequent involvement of the facial nerve and discrepancy between the high protein level and the lower number of cells in the cerebrospinal fluid, in those who have completed a course of antirabic treatment.

Immunization of animals.—In South America, cattle in many areas are being immunized prophylactically, while in certain towns dogs have been similarly treated. During the rabies outbreak in Singapore in 1937, arrangements were made to immunize the whole dog population, amounting to approximately 13,000. A killed virus should preferably be used for animal immunization.

Examination of suspected material for evidence of rabies.—The material generally consists of the head of some animal, most frequently of the dog, and should be wrapped in cloths soaked in bichloride of mercury or other germicidal solutions, while for miscroscopic examination material may be sent already fixed in weak alcohol. For inoculation, the medulla which has been immersed in glycerin is suitable. Sections give better results than smears, but naturally take longer to prepare. If grossly contaminated with bacteria, the tissues should be treated with ether in a concentration of 10 per cent., which does not destroy the virus when allowed to act for two hours at 4° C.

In order to locate the hippocampus, or cornu Ammonis, the brain is placed upwards, with the temporal lobe lifted outwards from the median line until the cornu comes into view as a long cylindrical whitish body tapering at its anterior end. Smears are made on slides or cover glasses by crushing a small section of brain matter between two of them and drawing out under gentle pressure to produce a fairly thin film. After fixation they are stained in Unna's polychrome methylene blue for three minutes and examined after differentiation in 95 per cent. alcohol. Negri bodies stained in this way take on a magenta colour. In recent years it has been suggested that the mesencephalon, or oculomotor nucleus, is a more favourable site than the hippocampus. Morgan and McKinnon, however, found that in naturally infected dogs and donkeys, the hippocampus should be regarded as the site of election.

Another technical method is subdural inoculation, which is performed by a small trephine or jeweller's drill, to effect an opening into the skull large enough to admit a needle. The mouse is more suitable than the rabbit or the guinea-pig. Negri bodies can be demonstrated in mouse brains eight to nine days after inoculation (Sulkin and Nagle).

For the technique of removal of the spinal cord from rabid rabbits and the methods of drying in vitro, more authoritative works must be consulted. The present dry method consists of cutting 1 cm. pieces of cords of rabbits killed each day after inoculation, up to the eighth day. These should then be placed in glycerin in a cold place, where they will retain their potency for several weeks. Material conserved in this way can be distributed from the laboratory. It is first cut into half-centimetre pieces, each of which serves for one injection, when emulsified in $2\frac{1}{2}$ ml. of salt solution.

CHAPTER XXI

DENGUE

Synonyms. Dandy Fever; Breakbone Fever; Chapenonada (Philippines); Sellar Fever.

Definition.—A specific fever conveyed by Aēdes ægypti, and some other aëdine mosquitoes, occurring usually as a rapidly spreading epidemic. Throughout the febrile stages, and often subsequently, severe rheumatic-like pains are prominent. The disease in its active form lasts about a week, and is attended with little, if any, mortality. Severe cases may simulate yellow fever.

Geographical distribution.—Europe.—Greece (epidemic of 239,000 cases in September, 1928), Turkey. Asia.—Syria, India, Ceylon, Burma, Cochin China, S. China, Indonesia, Philippines. Africa.—Egypt, Libya, Tunis, Morocco, Tangier; whole of coastline as far south as Loanda on the West and Durban on the East; Madagascar; Mauritius and other islands of the Indian Ocean. Australia.—N. Territories and N. Queensland (Brisbane), New Guinea, Fiji, Samoa and other Pacific Islands. America.—Central and S. America as far south as São Paulo in Brazil. N. America, Charleston and Philadelphia (epidemics in 1922–23 and again in 1934); W. Indian islands.

Epidemiology and endemiology.—The characteristic of dengue fever is its tendency to recur at intervals of years, sometimes in pandemic waves, during which, it may be, three-fourths of the population are attacked. The epidemic may last for one season, or may be spread over several years. Between them, sporadic cases occur, by means of which the virus is maintained. Thus is formed the nidus of infection for a new epidemic but, owing to their mild nature, sporadic cases are frequently not recognized. In pandemic form the disease often appears at a considerable distance beyond its usual confines, and may even ascend mountains to a height of 5,000 feet. The epidemiology appears to depend more upon conditions suited to the particular mosquito conveying the disease than upon those affecting man. Owing to the shortness of the immunity produced, control of dengue requires reduction of the mosquito index to zero.

When dengue spreads beyond its ordinary tropical limits, as for example in the epidemics of Philadelphia and Asia Minor, extension occurs only during the hottest part of the year—in the late summer and early autumn. Epidemics occur generally after the rainy season and, in the Pacific Islands, and in the southern hemisphere generally, the disease appears to

have a seasonal incidence during June, July, and August.

It appears to prefer the coast-line, and the deltas and valleys of great rivers, to the interior of continents. Nevertheless it may occur not only in tropical jungle, but in savannah country. The Grecian epidemic of 1928 was ascribed to the great increase of the population of Athens, and the establishment of a large non-immune community increased by a great influx of refugees. There were numerous breeding-places of mosquitoes in the Piræus, and it was estimated that 90 per cent. of the population became infected.

The observations of Mackerras in New Guinea suggest that there is a parallelism between the epidemiology of dengue and yellow fever in that "urban" and "jungle" forms can occur in both diseases. There the latter type is found over very wide areas and the distribution of A. scutellaris agrees exactly with that of dengue. The broad picture is of Aëdes ægypti-caused dengue in small parts of old-established settlements, and scutellaris-caused dengue in parts far removed from civilization.

Ætiology.—Graham, in Beirut, Syria, first suggested that the disease was transmitted by a mosquito (Culex fatigans). Later, Ashburn and Craig (1907) demonstrated that dengue is caused by a filterable virus which is not contagious, and that a true immunity to re-infection is developed in certain individuals.

By a series of well-conceived experiments, Cleland, Bradley and MacDonald in Australia proved that the virus of dengue is conveyed by one species—Aēdes æqupti (formerly Stegomuia fasciata), but not by Culex fatigans. By subinoculation from one individual to another they transmitted the disease for four generations, and showed that the virus is present in the blood from the second to the fourth day. Subsequent experiments by Siler confirmed this work. He found that the blood in dengue is infective to the mosquito from eighteen hours before onset to the end of the third day of the illness. A. æqupti does not become infective for eleven to fourteen days, but then remains so for the rest of its life. When the temperature is below 18° C. this does not occur. Passage of the virus through man to the mosquito fails either to attenuate or increase it. Simmons (1981) showed that Aëdes albopictus is probably the chief vector in the Philippines and probably also in Japan. In New Guinea the vector is A. scutellaris, subspecies hebrideus. The extrinsic period in these mosquitoes is between 13-19 days. Armigeres breinli may also be an efficient vector. In Florida, it has been suggested on epidemiological grounds that Aëdes tæniorhunchus may also transmit dengue.

Blanc and Caminopetros studied the epidemiology of dengue in Greece and Macedonia, and showed that in these countries its distribution and that of Aëdes ægypti correspond, but in Australia the distribution of dengue is always rather less extensive than that of this insect. An idea has been fostered that some affinity between the virus of dengue and that of yellow fever might exist, but this received no confirmation from the work of Stefanopoulo and others who subjected the sera of several individuals who had suffered from dengue to the yellow-fever mouseprotection test. Moreover, Dinger and Snijders fed mosquitoes (Aëdes albopictus) on dengue cases in Medan, Sumatra, and then dispatched them to Amsterdam, where they were re-fed on volunteers who subsequently developed dengue. It was thereby proved that the same virus in the same batch of mosquitoes reproduced different types of fever in different individuals. One might show the typical saddle-back temperature curve: another, continuous fever lasting seven days. From this they concluded that the five-day fever of Scheer and the seven-day of Rogers are not distinct diseases, as had been supposed.

Manoussakis has shown that the dengue virus can be transmitted almost

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indefinitely from one volunteer to another without alteration in virulence, and in each the incubation period was five to seven days. Twenty-five ml. of blood was taken from a dengue case in the first twenty-four hours of the disease, placed in 200 ml. of normal saline, sealed and placed in the incubator; after six days' incubation 6 ml. of the supernatant fluid, injected subcutaneously into volunteers, gave rise to dengue. The virus can be dried and frozen without losing its virulence. This was shown by Hoffmann, Mertens and Snijders, who transported dried serum from Java to Amsterdam and subsequently inoculated volunteers, reproducing typical fever 285 days after it had been abstracted.

The disease can be transmitted from man to various species of monkey: Macaca mulatta, M. philippensis, M. funicatus. In M. mulatta there is, as a rule, a leucopenia with reduction in the number of polymorphonuclear leucocytes. Though the virus is present in the blood, the disease cannot be transmitted from monkey to monkey. Mice are not susceptible to inoculation. The so-called cattle dengue, sometimes termed three-day or ephemeral fever, though also due to a virus, has no relation to human

dengue.

Sabin has found that one strain of dengue is transmissible to mice by intracerebral inoculation.

According to Pandit and Shortt, dengue virus has been cultivated in India on the chorio-allantoic membrane of the chick. By these means it was found that the virus persists in the blood for seven days. During convalescence immune bodies can also be demonstrated by this method.

Pathology.—On account of the low mortality post-mortem records are few. In the autopsies recorded, localized pulmonary and intracranial inflammation and general lymphadenitis were the special features. Serous effusions in the neighbourhood of joints and inflammation of the crucial ligament of the knee have been noted, while myocarditis, nephritic lesions with degeneration of the cells of the convoluted tubules, and a specific encephalitis with leucocytic blocking of some of the cerebral capillaries, have also been recorded.

Symptoms.—As noted by Findlay and Brookfield attacks in Europeans are more severe than in the indigenous inhabitants. The *incubation period* of the naturally acquired fever seems to be somewhat variable, generally from five to nine days, though sometimes it appears to be shorter. The course of the disease may be divided into three periods: stage of invasion, lasting two to three days; stage of remission, lasting twelve hours to three days; terminal fever and eruption.

Stage of invasion.—An attack of dengue may be preceded for a few hours by a feeling of malaise or, perhaps, by painful rheumatic-like twinges in a limb, toe, finger or joint, which, when confined to the knee-joint, are exeruciating. Usually it sets in quite suddenly. Sometimes the fever is ushered in by a feeling of chilliness or even by a smart rigor; sometimes a deep flushing of the face is the first sign. However introduced, the fever rapidly increases. The head and eyeballs ache excessively, and some particular limb or joint, or even the whole body, is racked with peculiar stiff, rheumatic-like pains, which, as the patient soon discovers, are much

aggravated by movement. The loins are the seat of great discomfort, amounting in some cases to actual pain; the face—particularly the lower part of the forehead, round the eyes, and over the malar bones—may become suffused a deep purple; and often the skin over a part or the whole of the body, and all visible mucous surfaces, are more or less flushed. The mouth and throat are usually erythematous with small superficial erosions. The eyes are usually much injected. This congested, hypersensitive and erythematous state of the skin constitutes the so-called prodromal eruption. There may be a tache cérébrale.

The cerebro-spinal fluid is under pressure; there is some increase in the albumin and a considerable increase in sugar, but no increase in the chlorides and no marked cellular reaction. This hypertension is probably the cause of the severe headache, stiffness of neck, pain in the back and bradycardia which supervene in the stage of reaction.

These symptoms becoming in severe cases intensified, the patient, in a few hours, is completely prostrated. His pulse rises to 120 or more; his temperature to 103° F. (Chart 20), in some cases to 105°, even to 106° F. He is unable to move owing to intense headache, severe pain in limbs and loins, and profound sense of febrile prostration. From time to time the skin may be moistened by an abortive perspiration, but for the most part it is hot and dry. Gastric oppression is apt to be urgent, and vomiting may occur. Gradually the tongue acquires a moist, creamy fur, which, as the fever progresses, tends to become dry and yellow. In this condition the patient may continue for from one to three or four days, the fever declining somewhat after the first day.

In a proportion of cases, and particularly in certain epidemics, crisis

does not occur, the fever slowly declining during a period of three or four days. In some epidemics enlargement of the lymph nodes, particularly of the cervical group, has been noted, especially by Helser (1937), and more recently by Findlay and Brookfield (1943) in the Gold Coast and Nigeria. In one epidemic in St. Thomas in the Virgin Islands adenitis was recorded in 62.5 per cent.

Stage of remission.—When the second stage is established and the thermometer has sunk to normal, the patient is sufficiently well to

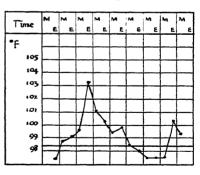


Chart 20.—Dengue. (After Cleland and Bradley.)

leave his bed and even to attend to business. The tongue clears, and the appetite and sense of well-being return to some extent.

Terminal fever and eruption.—The state of comparatively good health continues to the fourth, fifth, sixth or even to the seventh day, counting from the onset. Then there is generally a return of fever, slight in most cases, more severe in others. With the recurrence of the fever a rubeolar eruption, consisting of dark, dusky spots, appears. The pains likewise

return, perhaps in more than their original severity. Though the fever subsides in a few hours, the eruption, at times very evanescent, may be apparent for two or three days longer, to be followed very frequently by an imperfect furfuraceous desquamation.

Characters of the eruption.—The terminal rash of dengue possesses very definite characters. It is absent in a very few cases, but in many, being slight, it is overlooked. Usually it commences on the palms and backs of the hands, extending for a short distance up the forearms. It quickly extends, and is best seen on the back, chest, upper arms (Plate VII) and thighs. Here it appears at first as isolated, slightly elevated, circular, reddish-brown, rubeoloid spots, \$ to \$ in. in diameter, thickly scattered over the surface, each being isolated and surrounded by sound skin. There may be a general coalescence, isolating here and there patches of sound skin; in this case these give rise, at first sight, to the impression that they constitute the rash—a pale eruption, as it were, on a scarlet ground, giving an appearance "midway between scarlet fever and measles." The spots disappear on pressure, and never, or rarely, become petechial. Usually the face escapes. They fade in the order in which they appear—first on the wrist and hands; then on the thighs and body; lastly, on the legs and feet, but they may still be visible three weeks after recovery from fever. Desquamation may persist for two or three weeks. In many it is triffing: for the most part it is furfuraceous.

At this stage the characteristic slowing of the pulse, which may fall as low as 44 per minute, and leucopenia, which may reach 1,200 leucocytes, are noted; the latter is mostly due to a marked decrease of the polymorphonuclear cells, which may be reduced to 40 per cent. (with Schilling shift to the left), and to a relative increase of the lymphocytes (up to

53 per cent.).

Rheumatoid pains persist for some time after convalescence has been established. They are usually worse on getting out of bed and on moving the affected part after it has been at rest for some time, and are somewhat relieved by rest and warmth. In some cases a periarthritis of the knee-or ankle-joint supervenes and may cause considerable disablement, which does not clear up for months or years. Dengue pains persist in the small muscles of the hands and soles of the feet, probably located to the deep fascia. They eventually wear off. Complications are few. Albuminuria, parotitis, orchitis, herpes labialis and epistaxis have been recorded.

Convalescence may be much delayed by anorexia, general debility, mental depression, sleeplessness, evanescent feverish attacks, boils and

urticarial, lichenoid and papular eruptions.

In Europeans an attack of dengue very often leads to a condition of debility, necessitating temporary change of climate, or even return to Europe.

Variability of epidemic type.—Judging from the published descriptions, there is considerable variety in the symptoms of this disease in different places and in different epidemics. Some authors mention swelling and redness of one or more joints as a common and prominent symptom; others refer to metastases of the pains, enlargement of submaxillary glands,

general adenitis, mental depression, hæmorrhages, and so forth. However this may be, the essential symptoms in well-marked cases are the same practically everywhere and in all epidemics, viz., suddenness of the rise of temperature, an initial stage of skin congestion, limb and joint pains, and a terminal rubeoloid eruption. In a sudden outbreak in New Caledonia Mayrac recognized the following types:

(1) a simple febrile type with an urticarial rash;

(2) nervous type with intense headache;

(3) gastro-intestinal type;

(4) a type in which joint pains were the main feature.

These observations have been more or less confirmed by American medical officers in the South Pacific in 1943, 1944 (Diasio, Richardson, Kisner and Livansky).

As there are varieties of strains of every virus known it is highly probable there are different antigenic strains of dengue virus. This, as in the case of influenza, would account for the frequency with which persons who have had dengue more than once in one area go down immediately on going to live in another dengue area.

In the Athens epidemic, some of the following clinical manifestations were noted: gastro-intestinal disturbance, vomiting, epigastric pain, hiccup, hæmorrhage into skin and mucosa, and complications such as parotitis, otitis, furunculosis and broncho-pneumonia. In some acute cases with early and severe gastro-intestinal phenomena, bleeding from the gums and hæmatemesis were seen. Encephalitic symptoms have also been described. The spleen and liver are not enlarged.

In the American forces in the South Pacific "dengue orchitis" was recognized as a complication and sometimes atrophy ensued (Weyrauch and Guss).

Relapses are not uncommon in dengue, and second and even third attacks have been recorded. As a rule, however, susceptibility is exhausted by one attack.

Immunity.—Schule pointed out that certain of his volunteer American soldiers proved remarkably resistant to experimental inoculation with the dengue virus, and these were individuals who had been resident for some time in an epidemic area of the disease. Probably, immunity is due to previous mild attacks. The immunity in dengue does not last more than six months; it thus differs from that of yellow fever, which is life-long.

Mortality.—In uncomplicated dengue the mortality may be said to be almost nil (0·1 per cent., Hare). During the 1928 epidemic in Greece Cardamitis gave the mortality-rate as 1 in 61,000.

Diagnosis.—Dengue must not be confounded with yellow fever, Rift Valley fever, rubeola, scarlatina, measles, Colorado tick fever, Bullis fever, syphilitic roseola, influenza, cerebro-spinal meningitis, typhus, hæmorrhagic smallpox, enteric, phlebotomus fever, seven-day fever (leptospirosis), rheumatic or malarial fever. A knowledge of the distinctive features of these diseases, and the fact that dengue is attended with a rash and with articular pains, and that it occurs in great and rapidly spreading epidemics, should prevent any serious error. A complement-fixation test has been

devised (Sabin and Young). The antigen is extracted with benzene from the brains of 3-14 day old mice inoculated intracerebrally with a dengue virus exalted in virulence by repeated passages through baby mice.

Using this antigen, complement-fixation titres of 1:64 to 1:256 were obtained in human volunteers within 2-6 weeks of inoculation, and also in rhesus monkeys and chimpanzees injected with homologous strains of the virus. Within six months reaction became negative.

Treatment.—Were it possible to secure perfect isolation and immunity from mosquito-bite for the individual during an epidemic of dengue, doubtless he would escape the disease. Even comparative isolation is attended with diminished liability. There is no specific treatment.

Like the allied fevers, dengue runs a definite course; therefore it is useless to attempt to cut it short. The patient should go to bed as soon as he feels ill, and should keep to his room until the terminal eruption has quite disappeared and he feels well again. Ten days is not too long to allow in severe attacks. As in influenza, light liquid diet, rest, and the avoidance of chill conduce powerfully to a speedy and sound convalescence. At the outset of the fever some saline diaphoretic mixture, with aconite, may be prescribed with advantage. If the pains be severe and the fever high. antipyrin, phenacetin, belladonna, or vinum colchici (15 min. t.d.s.) give great relief. Cold applications to the head are comforting. If the temperature rises to 105° F. or over, cold sponging or the cold bath ought to be used. If the pains continue very distressing, a hypodermic injection of a minute dose $(\frac{1}{10}$ gr.) of morphia will afford welcome relief and do no harm. Purgatives and emetics should be avoided, unless pronounced constination, or a history of surfeit, urgently demands their exhibition. The pain caused by the muscular movements entailed by purgatives more than counterbalances any advantage. In the Athens outbreak, urotropine in full doses was given in the early stages and, if pains were severe, aspirin, amidopyrine and caffeine. For cerebral symptoms, which in some patients might be an important feature, bromides and strophanthus are indicated. Alcohol in the early stage is not advisable. Freshly-made lemonade, or iced water, will be acceptable during the fever.

For the pains experienced during convalescence, rubbing with opium or belladonna liniment, gentle massage, electricity, salicylates, and small doses of iodide of potassium have been advocated. Debility or anorexia indicate tonics, such as quinine, strychnine, mineral acids or vegetable bitters and

change of air.

Prophylaxis is the same as for yellow fever and for other mosquitoborne diseases, and is directed against infected mosquitoes.

Prophylactic inoculation.—St. John and Holt attempted to produce a dengue vaccine. Vaccine made from the liver and spleen of dengue-infected monkeys did not protect volunteers from an attack; but there was evidence that the disease became mitigated in the inoculated.

CHAPTER XXII

COLORADO TICK FEVER, BULLIS, EPIDEMIC HÆMORRHAGIC AND IZUMI FEVERS

In 1930 Becker described a disease called Colorado tick fever which up to that time had been assumed to be a mild form of Rocky Mountain spotted fever. The disease is associated with the bite of the wood tick, Dermacentor andersoni, but evidence that infection is transmitted by the tick is largely circumstantial. The virus will pass through a membrane of pore size $24 m \mu$, and is thus one of the smaller viruses. The incubation period is four to six days and there is usually a sudden onset with chilly sensations, generalized aching, headache, post-ocular pain and lumbar backache. A temperature of between 102° and 104° F. is usually attained within twenty-four hours and is associated with an increased pulse rate. This attack lasts two days and is followed by a symptom-free interval of the same duration with a subnormal temperature. The second attack lasts about as long as the first or a day longer and may be more or less severe than the first. Single or triple attacks have been reported, but are rare. Apart from a mild erythema and slight conjunctival injection there are no physical signs and complications and death have not been recorded. There is a leucopenia involving all white cells except the monocytes. Colorado tick fever is not unlike Rocky Mountain spotted fever and dengue, but those who are immune to Rocky Mountain fever and dengue can be inoculated with Colorado tick fever. Bullis fever and Colorado tick fever do not cross immunize in human experiments. The disease has been transmitted to golden hamsters which after twelve or more passages succumb to infection. The disease can be passaged intracerebrally in mice and in the developing chick embryo. A formolized chick embryo vaccine is being tested in man. Oliphant and Tibbs (1950) isolated the virus from the blood of ten patients and then inoculated Swiss mice 3-5 days old. The virus was present in the blood from the first to tenth day of illness. Some difficulty was experienced in adapting strains to older mice, but eventually success was obtained by intraperitoneal and intracerebral passage. The strains were verified by neutralization tests against immune sera of hamsters originally infected by the strain of the virus.

It is probable that this disease is not confined to Colorado and it is possibly a tick-borne dengue. If so then its relationship to mosquito-borne dengue would be analogous to that between tick-borne and louse-borne typhus.

BULLIS FEVER (LONE STAR FEVER1)

A new form of fever appeared in Texas in the spring and summer of 1942 in soldiers engaged in field exercises at Camp Bullis, near Houston, Texas. All patients had multiple tick bites by Amblyomma americanum shortly before the onset. The fever lasted from 3 to 13 days in a series of 33 cases. The onset was abrupt, with post-orbital and occipital headache, and the fall of fever was by lysis. General adenopathy was common. In the more severe attacks, a maculo-papular rash appeared on the trunk, in some resembling murine typhus, in others like German measles; it never lasted more than 48 hours. On the second or third day there was pronounced leucopenia, with associated neutropenia (Woodland, McDowell and Richards, 1943). Later, Anigstein and Bader (1943) isolated, from a collection of Amblyomma americanum, a virus which was established in guinea-pigs.

Febrile response in animals varied (Anigstein and Bader) producing one-day fever after 12 days, febrile spells of one or two days, continued high, irregular

14. americanum is popularly known as the "Lone Star tick" from the bright spot on the scutellum of the female tick. or protracted low fever. The spleen is always enlarged. This outbreak has more than local importance and serves as a warning that when bodies of troops are engaged in areas infested with ticks or mites, outbreaks of disease transmitted by these arthropods may be expected. It may even be that it is the same entity as Colorado tick fever.

EPIDEMIC HÆMORRHAGIC FEVER

Synonyms "Red fever of Korea," Songo fever, Kokka disease, Korin fever, Nidoko disease: names reminiscent of places where some of the earlier outbreaks have occurred. The fever resembles "scrub typhus" in its epidemiology, but the clinical features differ considerably. It was known to the Russians in Manchuria in 1938 and to the Japanese in Korea towards the close of the Second World War and cases had been reported in Japanese medical literature. It is generally considered to be a virus disease transmitted to man by the mite—Lælaps jettnuri, Vitzthum. The host of this mite and probably also the reservoir of the virus is a field mouse—Apodemus agrarius.

In clinical features it presents considerable differences from the typhus group. The disease is characterized by fever, myalgia, albuminuria and a petechial rash. In more severe cases hæmoptysis, hæmatemesis, hæmaturia, and melæna may occur. The onset is usually abrupt. Conjunctival hæmorrhages are frequent, except in the first three days, but the pain and photophobia lead the patient to close the eyes or to shade them, whilst the slight ædema of the upper lids gives the patient a bleary-eyed appearance, resembling measles without lacrymation. Retro-orbital pain, backache, severe anorexia, nausea and emesis suggest the diagnosis. The intense erythematous blush of the face and neck are due to toxicity, whilst the conjunctival and pharyngeal injection are out of proportion to any pharyngeal symptoms. The pulse is rapid and bloodpressure may be imperceptible. Death is due to peripheral vascular collapse. The urinary findings closely resemble those of acute glomerular nephritis. The tubular injury results in varying degrees of oliguria which can be accounted for by anoxia. Albuminuria is associated with large numbers of oval bodies in the urine which represent mononuclear cells and renal tubular cells (Ganong). These changes are primarily due to capillary fragility. Albuminuria, 1-4 plus. appears from 28-72 hours from the onset and persists for one week. The specific gravity falls to 1005. Pathological changes consist of cedema, congestion and hæmorrhages. These phenomena are most conspicuous in the anterior pituitary, kidneys and R atrium of the heart. The kidneys are so considerably involved as to be diagnostic. The cortex is sharply demarcated from the medulla, where hæmorrhages and a peculiar type of necrosis are present. Fever usually lasts about seven days and in favourable cases there may be complete recovery within fourteen days of onset, but in others a low-grade fever, palpitations, insomnia and anorexia may persist for some weeks. The fatality rate in Japanese hands was about 13 per cent. The fever has a seasonal incidence and is most frequent in May, June, October and November. Over three hundred suspected cases have been reported amongst troops in Korea and the mortality has been less than 10 per cent. See Ann. Int. Med. (1953) 38.1; U.S. Navy Med. News (1952) 20.2; U.S. Armed Forces Med. J. (1952) 3.11. Hullinghorst, Steer, Hornisher-Kessler.

Treatment is symptomatic. Antibiotics and sulphonamides are ineffective. Transfusion of blood from convalescents appears to shorten the duration of the fever. Fluids of any kind, oral or intravenous, must be given in small amounts, because of increased capillary permeability. They increase the cedema. The maximum amount should be that of the urinary output, plus 500 ml. to cover insensible loss.

Epidemic hæmorrhagic fever has to be differentiated from relapsing fever, purpura, leptospirosis and typhus. In Russia what is known as alimentary toxic aleukia is due to eating diseased grain infected with the fungus, Fusarium sporotrichoides. Other hæmorrhagic fevers are Crimean, said to be transmitted by the tick, Hyalomma marginatum; Omsk hæmorrhagic fever is carried by the tick Dermacenton pictus, but both of these fevers do not develop nephritic complications. Hæmorrhagic fever in Bukovina is transmitted by Ixodes ricinus and is probably the same as the foregoing. Others from Uzbekistan and Turkmenistan resemble the epidemic hæmorrhagic disease very closely.

Prophylaxis.—Should the Japanese account of the ætiology be correct this should be the same as that for mite or "scrub" typhus.

IZUMI FEVER (Japan)

Since Prof. Izumi first described a sudden outbreak of a scarlatina-like disease in the town of Kanagawa in 1927, over one hundred outbreaks have been reported. It is now recognized as constituting an independent disease in its clinical aspects, though the specific cause has not yet been ascertained.

Now Nishioka and Morita (1952) have studied a sudden outbreak in a fishing village in the Sakishima district of the Shima peninsula, S. of Tokyo, in 1951, where epidemiological investigations revealed that it was due to drinking spring water. This fever occurs both sporadically and in epidemics. Secondary, or case-to-case, infections are very uncommon.

Clinically the fever is characterized by a rash, typical temperature chart and gastro-intestinal disturbances. There is a severe form showing biphasic fever and lasting up to three weeks, and a mild form which exhibits one peak of fever and a relatively short course. The incubation period is 5–13 days, whilst the onset is abrupt with a temperature of 103° F. to 104° F. Joint pains, lumbar pains, nausea, vomiting and anorexia are common.

The rash which is pathognomonic appears on the first and second days, often with itching, and is described as being intermediate between that of scarlet fever and measles. Slightly elevated miliary papules appear on the flushed skin; later becoming dark red and disappearing in 3-4 days. The trunk, face, neck and extremities are attacked. In mild cases recovery then ensues, but most, after an interval of 1-2 days, suffer from a second attack with rise of temperature to 104° F. and a secondary rash which is confluent and of the macular type, with recurrence of gastro-intestinal symptoms. There then ensue periods of intensive sweating and in some the fever gradually remits and the temperature becomes normal after 4-5 weeks. Desquamation begins as a fine scaling of the body, usually on the tenth day, and is completed during the fourth or fifth week. Enlargement of the liver is noted in one-third and the urine usually contains urobilinogen. Twenty-one had sore throats and 23 per cent. showed "strawberry tongue." Circumoral pallor was not distinct. In treatment aureomycin gave the most satisfactory results.

From the studies of Kumada, Sasa, Miura and Nishioka evidence was obtained, from the epidemiological standpoint, that Japanese field mice—Apodemus speciosus—may constitute the reservoir of the hypothetical virus by polluting by urine and fæces the water sources where outbreaks of the disease occurred.

CHAPTER XXIII

PHLEBOTOMUS FEVER

Synonyms. Papataci Fever; Three-day Fever; Sandfly Fever, "Dog Disease," "Hundfieber," "Russian Headache Fever," Bessarabia Fever (Boehnhardt).

Definition.—A specific fever of short duration and no mortality caused by a virus introduced by the bite of a sandfly (*Phlebotomus*).

Geographical and seasonal distribution.—Coextensive with that of insect transmitter (*Phlebotomus*). Absent in Bermuda where no sandflies are found. In tropics occurs as epidemics amongst new arrivals; sometimes 75 per cent. are attacked. Natives of endemic area appear to be immune. In subtropics it principally occurs during summer and autumn. Sandfly fever was common in wars of 1914–1918, 1939–1945 in Mediterranean—Malta, Gallipoli, Ægean islands. Widespread in Egypt, Sudan, Palestine, Syria, Iraq, Persia and India, S. China. Common in Africa with exception of W. and E. Africa; Red Sea provinces and Arabia, and Persian Gulf. In America, N. Argentine, N. Brazil, Panama and some West Indian islands. In Caucasus, Chitral and Himalayas it is found up to 4,000 ft.

Epidemiology.—In Palestine and Syria spring and autumn outbreaks are common. In Malta the peak period is in July, falling gradually to the second week in November. Two waves occur, each lasting 3-4 weeks. The first at commencement of the hot weather, the second in the autumn, being due to the second brood of sandflies. The eight weeks between the epidemic peaks is the approximate time required by *P. papatasii* to complete its life cycle.

Ætiology.—The virus resides in the patient's blood during the first two days of the fever. It is ultramicroscopic, passing through filters which arrest Brucella melitensis. According to Doerr, the virus may be transmitted hereditarily through the egg and larva of phlebotomus to the imago, and this has been confirmed by Mochkovski and Diomina. The infection is transmitted by the bite of female sandflies of the second generation hatched from eggs laid 6-8 days after the infecting feed. Infection has been produced by the bites of newly-hatched sandflies. A short sharp fever has been produced in monkeys after intravenous injection of sandfly-fever Little is yet known of the physical properties of the virus. According to Whittingham, it may survive the winter, either free in the soil, or within the bodies of phlebotomus larvæ, which inhabit such sites as moist soil and porous walls. If this is correct, then it is the only instance in which an animal virus has been transmitted hereditarily by an insect vector, but may be an important epidemiological consideration and explain the suddenness and extent of outbreaks of sandfly fever in India and North Africa in the spring.

Shortt, Poole and Stephens showed that, as with dengue, the sandfly-fever virus can pass through L_3 and L_5 Chamberland filters, and that it

is present in the highest concentration in the blood during the first and second day of the disease. They proved that it can survive outside the body for sixty hours. Shortt, Pandit, Anderson and Rao cultured the virus on the chorio-allantoic membrane of the chick embryo; by subsequent inoculation it could be demonstrated in monkeys for an average of 11 days, and subsequently immune bodies up to 69 days. According to Russian workers the virus causes a proliferative necrosis of the chorio-allantois. It can be inactivated by treatment with commercial formalin, 1 in 1000, and it can be dried and preserved in a vacuum desiccator for eight months.

In cases of fever and in convalescents the presence of the virus in the blood can be demonstrated by egg-culture up to three or four weeks

from the onset of fever.

Representatives of the genus *Phlebotomus* are to be found in most tropical and subtropical countries. The various species are usually designated "sandflies." They are exceedingly minute, very delicate, greyish, or brownish, somewhat slenderly-built insects that bite principally during the night and that can pass easily through the meshes of an ordinary mosquito-net. The powers of flight are feeble; more usually the insects progress by a series of short skips.

It must be emphasized that not all species of phlebotomus transmit the disease, only, as far as is known, *P. papatasii*. There are many species of

sandfly in Africa in places where there is no sandfly fever.

P. papatasii, the species on which Doerr's observations were made (hence one of the names for the disease, papataci fever), lays about forty eggs, selecting for the purpose damp localities such as the walls of cellars, of latrines, cesspools, crevices in walls, caves, and embankments. The cycle of egg, larva and imago takes about one month in warm and upwards of two months in cooler weather (see pp. 1016, 1018). It has not been determined which of the many species of phlebotomus, other than P. papatasii, conveys this fever. The insect can transmit the infection after an incubation period of six days.

Pathology.—Dengue and phlebotomus fever have several important points in common, a circumstance suggesting the possibility of a common or, at all events, a similar origin. Each is transmitted by an insect; the viruses occur in the blood-stream and are filterable; they are diseases of warm climates only; and clinically, they are characterized by a short incubation period and a brief and rapidly developed fever which is usually associated with relatively slow pulse and leucopenia, and relative decrease of the polymorphonuclears. There is no evidence that these diseases are mutually protective. The post-mortem appearances of sandfly fever are unknown.

Symptoms.—The bites of the infected sandfly occasion a considerable amount of irritation, resulting in hyperæmia and even in ædema. After an incubation period of from four to seven days, with or without a prodromal stage, the fever is ushered in suddenly by slight or more severe rigor with a temperature of 102° F. which may reach 105° F. In 10 per cent. there is a short secondary rise. The face becomes flushed and swollen, frontal headache is intense, and there is usually severe general aching and stiffness in the back of the neck. Agonizing photophobia, accentuated by pressure on the globes or by the least movement of the head, is characteristic. Supraorbital headache is also quite common. There are influenzal pains in the back and legs and general stiffness of the muscles. More rarely the

pain is referred to the epigastrium. A sense of band-like constriction round the lower part of the thorax is sometimes so prominent as to resemble epidemic pleurodynia, or Bornholm disease. The patient is drowsy, but suffers from insomnia. The conjunctive are so injected that the eyes have been compared to those of a mastiff. The tongue has a central fur. The fauces and palate are often congested, and are studded with small vesicles; it has been remarked that they are devoid of any surrounding mucosal inflammation. The vesicles are not strictly peculiar to sandfly fever as they have also been noted in infective hepatitis. In from twenty-four to

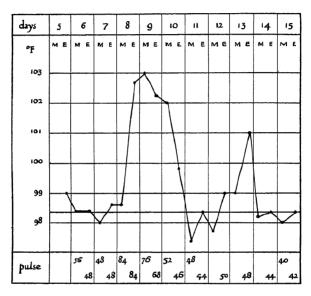


Chart 21.—Phlebotomus fever showing prodromal period, typical attack, recrudescence and bradycardia. (Lambert, Jl. Roy. Nav. Med. Ser.)

thirty-six hours the temperature has reached 103-104° F. (Chart 21). It keeps about this point for a day longer, and then begins to fall, with or without epistaxis, vomiting, sweating and diarrhea, reaching the normal about the end of the third or beginning of the fourth day. The patient continues debilitated, especially mentally, for a week or two longer. According to Lambert, the name "three-day fever," applied to the disease, is misleading, since the pyrexial period may occasionally vary from two to eight days. In some cases there are several days of apyrexia followed by a secondary rise of temperature lasting a day or two.

The blood-picture shows a slight leucopenia, without serious alteration in the proportion of mononuclears, especially from the second to fourth day, after which there is a leucocytosis of 15,000-20,000. The pulse-rate s relatively slow. Relative bradycardia is noticeable by the second day

of the disease, as soon as the patient complains of headache, and is possibly due to increased pressure of the cerebro-spinal fluid. An absolute bradycardia is noted at the end of the fever.

Le Gac and Albrand first recorded that the cerebro-spinal fluid is under increased pressure and that it contains from 10 to 110 lymphocytes per cu.mm. Albumin is always increased and the chlorides slightly decreased. These findings have been amply confirmed.

Shee (1942) described varying degrees of choking of the optic disc, ranging from blurring of the edges to papilledema. This was seen in the

early stages, but in severe cases was visible at the crisis.

No serious complications occur, but in some years diarrhea, in others pharyngitis, are features of the disease. Constipation, vomiting and stiffness of the muscles at the back of the neck are not uncommon. Second attacks are by no means rare, but are milder, and third and fourth attacks have been recorded. Shortt proved that immunity may sometimes persist for one year after an attack. On the whole, children suffer less severely than adults. It is hardly necessary to state the importance of distinguishing sandfly fever from abortive cases of acute poliomyelitis which may occur sporadically in sandfly fever districts.

Pearson (1941) drew attention to the similarity of benign lymphocytic meningitis and sandfly fever. There seemed to be in Palestine some connection between the incidence curve of the two. The cardinal signs of sandfly fever—frontal headache, orbital pain, photophobia, pains in the back, fever and conjunctival congestion—are duplicated in benign lymphocytic meningitis. The debility which ensues in some individuals is quite out of proportion to the intensity and duration of the initial attack. Acute synovitis as a complication has been observed in Iraq during the recent war. The mortality is nil.

Attention has quite recently been drawn to a dermatitis, known as "Harara" (i.e. heat), which is common in Anatolia, Syria and Palestine during the sandfly season, and is a reaction due to their bites. It is also stated that infected sandfly bites are the most painful.

Immunity is short-lived and second attacks occur in about 10 per cent., third attacks in 0.8 per cent. Certain individuals may suffer from several attacks in the same epidemic. There appears to be a high degree of immunity in the inhabitants of endemic areas.

Sandfly fever nets are of such small mesh that they are insufferably hot, and in Malta during the 1989-1945 war were replaced effectively by wide mesh nets impregnated with DDT.

Diagnosis.—It is extremely difficult in the early stages to distinguish this fever on clinical grounds from malaria (especially subtertian), from paratyphoid, dengue, typhus and influenza. In typhus the greater hebetude, and in influenza the respiratory catarrh, must be taken into consideration.

In Syria during the war years there was often some difficulty in distinguishing between the prodromal stage of infective hepatitis and sandfly fever.

Treatment.—The most valuable drug in the treatment of sandfly fever is opium; 30 drops of the liquor opii sedativus may be given at the onset. It greatly relieves the headache. Quinine is useless. Tincture of iodine should be applied to the bite. The headache has been relieved by lumbar puncture and removal of 5 ml. of fluid. Whenever possible, patients should be nursed under sandfly nets.

Prophylaxis.—As phlebotomus fever appears to be a disease of locality, houses and places believed to be infected should be avoided and, where possible, disinfected.

To diminish the local sandfly pest, all rubbish should be burned or otherwise got rid of, ruinous walls demolished, cracks in walls filled in with tar or mortar, latrines smoked with sulphur fumes, put into sanitary condition, and dark damp places dried, whitewashed, and ventilated, No gardens or cultivated ground should be permitted in the immediate vicinity of buildings. Creepers should not be allowed to grow on barrack walls. Benzene polychlorines, widely used in agriculture, are useful for destruction of sandfly larvæ, and are applied in solution in the strength of 75 ml. to every square metre. The adult flies can be killed in numbers by "swatting." By these and similar measures much can be done to control the infection. Unfortunately, a net having a mesh sufficiently small (i.e., 45 holes to the inch) to keep out sandflies is intolerable to a white man in a hot climate. As the phlebotomus does not fly higher than 10 ft., removal to an upper story is a very effectual preventive measure. Flit and DDT are the best sprays for destroying adult sandflies. Special staffs are necessary for the daily destruction of these insects in dwellings (see p. 864). Dimethyl phthalate is the best repellent.

To reduce the incidence of sandfly-bites general measures should be instituted. Shorts should not be worn after sundown, wrists and ankles should be smeared either with thymol ointment, or with "vermijelli," or oil of citronella. Wellington boots afford a good protection to legs and ankles after dusk. During the recent war in the Middle East, it has been found that blackout conditions increase the liability to sandfly-bites, because men prefer to sit outside, rather than in tents or huts.

Air-currents have a marked effect on sandflies, and Whittingham showed that the most effective way of ridding quarters of these pests is to create a strong current by electric fans.

Shortt and his colleagues used the cultural virus as a vaccine. In inoculated volunteers immune bodies in the serum were subsequently demonstrated.

CHAPTER XXIV

THE POCK DISEASES

At the present time classical smallpox is largely restricted to tropical and subtropical countries, where the preventive measures responsible for the decline of this disease in temperate climates are more difficult to enforce. In India and Pakistan, for example, the number of cases of variola reported during the year 1938 was 82,640, with a mortality of 27 per cent. During the same period there were severe outbreaks in China (Hong Kong and Shanghai) and in Nigeria; and a mild form of the disease with no fatalities was prevalent in the southern states of the United States.

During the last few years much has been learnt about the nature and properties of the causal agents of the pock diseases. The greater part of this work has been carried out with vaccinia, and it is therefore necessary to define at the outset the relationship between this virus and variola. That smallpox and all the animal pock diseases are closely related is certain. There are two possibilities: (1) a primitive mammalian pox has given rise to variola and alastrim in man, cow, horse, camel, sheep, goat and rabbit pox and also the disease of mice known as ectromelia, or (2) human pox has infected man's domestic animals or those animals closely associated with man giving rise to specific varieties of pox. Human pox and that of the horse, sheep, goat and possibly camel can be adapted to the calf giving rise to vaccinial variants. All the vaccinial strains now used for immunization are derived from variola, either through the calf or sheep or by inoculation into monkeys and thence on to rabbits. Vaccinia derived from variola is more virulent for the rabbit and calf than for man, while variola is more virulent for man than for the rabbit or calf. There is no close relationship between vaccinia and true cow-pox, which latter disease can be transmitted to persons immune to vaccinia. transition from variola to vaccinia is, fortunately, not reversible, so that once a strain of virus has been adapted to the calf or sheep it can be inoculated into man, producing in him a mild illness which renders him subsequently immune to the virulent parent form—smallpox. On rare occasions vaccination gives rise to a generalized papular or vesicular eruption with severe constitutional symptoms which may terminate fatally. This condition is believed to be due to an abnormal susceptibility to vaccinia, and not to an increase in virulence of the virus.

Nature and properties of the causal agent.—The infective agent of vaccinia is a round body, measuring about 170 to 250 $m\mu$ in diameter, to which the noncommittal term "elementary body" is applied pending the settlement by further research of the much-disputed question whether viruses should be regarded as micro-organisms or macro-molecules. These bodies were first seen and described in 1887 by Dr. John Buist of Edinburgh, who found them in the vesicle fluid of smallpox and vaccinia. In 1906 they were rediscovered by Paschen and are frequently referred to as "Paschen bodies." It is only during the last few years, however, that the bodies have been proved to be the causal agents. Methods have now been evolved of

preparing pure suspensions of the elementary bodies from the skin lesions produced in rabbits and sheep by specially-selected strains of vaccinia virus. These pure suspensions have been employed in recent studies of the physical, chemical and biological properties of the virus, and they are also being used experimentally in place of crude lymph for prophylactic immunization against smallpox. Chemical analysis has shown that the elementary body is composed mainly of nucleo-protein together with a carbohydrate and a lipoid fraction. Highly-purified suspensions of the elementary bodies contain phosphatase and catalase, and these enzymes are believed to be inherent in the virus; no dehydrogenase activity has been demonstrated. Copper and riboflavin are also present. Sedimentation photographs of elementary body suspensions, obtained with the Svedberg centrifuge, show fairly well-defined boundaries, indicating that the variation in size of the particles is very small. The bodies have an unusually high charge and electrophoretic mobility; they are also exceptionally sensitive to flocculation by salts. Although their size is below the limit of optical resolution for visible light, they can readily be seen with the dark-ground microscope.

When inoculated by inunction into the skin, the elementary bodies penetrate the cytoplasm of the epidermal cells and there proceed to increase in number, thus producing, perhaps with the addition of material derived from the infected cell, the so-called acidophil inclusion body which was described long ago by Guarnieri. The virus within the cells causes them to increase in size and also to proliferate freely. This increase in thickness of the epidermis, together with edema and hyperæmia of the subjecent dermis, is responsible for the papule. Later, the cells forming the centre of the papule degenerate and liquefy, thus producing the characteristic vesicle, in the fluid contents of which the elementary bodies are found in enormous numbers. The vesicle is rapidly converted into a pustule by the immigration of inflammatory cells, mainly polymorphonuclears, derived from the dermis. The fluid provides an excellent culture medium for staphylococci and other organisms, and the leucocytic response is largely due to this secondary infection. In non-fatal cases the crusts or scabs. which separate after the pustule has dried, contain active virus. The high infectivity of smallpox, however, is probably not due to dissemination of the crusts, but to lesions present in the mouth, throat and lungs. The expired air of patients suffering from variola has been shown experimentally to contain elementary bodies. The air in the vicinity of the patient thus becomes charged with microscopic droplets of water which he has exhaled. These droplets evaporate, leaving the elementary bodies suspended in the air where, being so minute, they may remain for long periods. A susceptible person breathing such contaminated air becomes readily infected. Contact with fomites is undoubtedly responsible for some infections, but the epidemiological characters of the disease can only be fully explained by the assumption that the virus is air-borne.

Vaccinia and variola, in common with other viruses, cannot be cultivated in the absence of living susceptible cells. The virus can be grown readily in tissue cultures of rabbit testis or corneal epithelium, and proliferation also takes place in a fluid medium consisting of rabbit serum and Tyrode's

solution to which small amounts of minced rabbit kidney or testis have been added. Vaccinia also grows without difficulty when implanted on the chorio-allantoic membrane or yolk sac of the developing chick embryo. Both these methods have been used successfully to procure a supply of bacteria-free virus material for prophylactic immunization. This culture virus may be inoculated by scarification in the usual way, or it may be injected intracutaneously. The latter method has the advantage of leaving no scar, but since a vaccination scar is the one infallible sign that a person has been immunized against smallpox, it would increase the difficulties of controlling an epidemic, especially among coloured races. There is evidence that strains which have been grown in vitro, or on the egg membrane for a long time, become attenuated so that they may fail to induce a good immunity when inoculated into man. Generalized vaccinia has been known to occur as the result of vaccination with virus grown on the chick embryo, and in addition the danger of sensitivity to egg proteins must be remembered. Whereas all strains of vaccinia virus tested appear to be antigenically similar, there is still some doubt as to the exact antigenic relationship of vaccinia and virulent strains of smallpox. The vaccinia virus is antigenically complex and contains three, possibly four, distinct antigens.

Laboratory diagnosis.—Elementary bodies can readily be demonstrated in the vesicle fluid by the dark-ground microscope. ¹The technique is the same as that for the detection of spirochætes. Permanent preparations are best prepared by using Gutstein's method:

Solutions needed.—(a) 1 per cent. methyl violet in distilled water.
(b) 2 per cent. NaHCO₃.

Technique.—A drop of the vesicle fluid is spread on a perfectly clean microscopic slide as for a blood film. Films are dried in the air, or in an incubator, and rinsed in physiological saline and then with distilled water. When dried, the film is fixed in methyl alcohol (or ethyl alcohol) for half an hour or more and the slide put in a dry Petri dish. Equal parts of solutions (a) and (b) are mixed in a test tube, filtered at once on to a slide, covered with a lid and incubated at 37° C. for twenty to thirty minutes. Rinsed in distilled water, they are dried and mounted in cedarwood oil or liquid paraffin. The elementary bodies are stained distinctly and intensely a light violet colour.

Finding elementary bodies in the vesicle fluid is of no value in differentiating smallpox from varicella, since the infective agent of the latter disease also takes the form of elementary bodies, and the two viruses are indistinguishable under the microscope.

The best methods for the diagnosis of smallpox are: (1) complement fixation, using a suspension of the crusts as antigen, and (2) implantation of smallpox virus on the chorio-allantoic membrane of the developing chick embryo. The first test takes 24 hours, the second three days. Downie's flocculation test is also widely employed.

¹ Van Rooyen and Illingworth (1944), however, confirmed Paschen's observation that the elementary bodies of variola are larger than those of varicella, and are easily demonstrated in the papular and vesicular stages. They have utilized this finding to form the basis of a laboratory test for smallpox.

The serum of a patient who is recovering from an attack of smallpox contains agglutinins which react specifically with various elementary bodies. These antibodies are not present in detectable amounts until the second week of the disease, and the reaction is therefore of little diagnostic value.

Serological methods have so far failed to discover any antigenic difference between variola major and variola minor. It is thus evident that the diagnosis of smallpox must be made mainly by clinical methods, but that laboratory tests may be of use in doubtful cases.

THE TECHNIQUE OF VACCINATION

In performing vaccinations in the tropics it is important to remember that exposure of the recently vaccinated arm to the rays of the sun rapidly inactivates the virus. Persons who have been vaccinated should be kept in the shade for at least half an hour and should be watched to see that they do not remove the vaccinia by licking or sucking the scarified area. A lesion closely resembling a vaccination is made by rubbing in the juice of the cachou nut into a lightly scarified area.

In recording the results of vaccination a redness coming on in from 24 to 48 hours after vaccination with itching must not be taken as a reaction of immunity. It may be caused by killed vaccine or by sensitivity to proteins in the vaccine. The only positive reaction is a distinct raised papule coming on in three or four days after vaccination and, if possible, going on to a pustule. If an allergic reaction alone is produced, vaccination should be repeated in a fortnight's time, preferably with a different batch of vaccine. Vaccine virus should be kept in the cold. Vaccinial encephalomyelitis is rare in the tropics, but cases have been recorded.

THE TREATMENT OF VARIOLA

The mortality from smallpox, excluding the severe toxic and hæmorrhagic forms of the disease, is largely due to secondary pyogenic infection of the respiratory tract. Energetic measures to combat this secondary infection should be commenced at an early stage. The sulphonamides are highly-effective chemotherapeutic agents against streptococcal infections. and this form of treatment has proved of great value in smallpox. Although sulphonamides have no action on the vaccinia virus they undoubtedly serve to control secondary bacterial infection. Sulphadiazine is the best: it should be given in full doses and the patient must drink large amounts Sulphonamides used solely as a dusting powder are quite useless. Penicillin injections may be given to control secondary infections: they are free from the disadvantages attending sulphonamide treatment. has recently been found that while pure penicillin has no effect on the pox viruses, impure penicillin after being boiled does have a direct action on the virus. Drug treatment should possibly be combined with the injection of large doses of concentrated multivalent antistreptococcal serum.

ALASTRIM

Synonyms.—Amaas; Kaffir milkpox; West Indian modified smallpox; parasmallpox; variola minor.

Definition.—This disease has been noted by many writers in the West Indies and South Africa.

The name is derived from the Spanish alaster, meaning to scatter or strew over (referring to the distribution of the rash). It is a disease of little or no mortality, and resembles smallpox in its mitigated form. Indeed, the individual case of this disease is clinically identical with a mild case of smallpox; they can only be distinguished one from the other in the mass.

Geographical distribution.—The disease has been recorded from the West Indies, South and Central America (especially Brazil), Africa, the Mediterranean area, and during the last 30 years from time to time in Great Britain. The most noteworthy epidemic was in Trinidad in 1902.

Epidemiology.—A striking difference between classical smallpox and alastrim is seen in the rate of progress through an unvaccinated community. Smallpox becomes rapidly epidemic, whereas alastrim can only be said to "smoulder," alternately waxing and waning, but never attaining really epidemic proportions. This, no doubt, depends upon the infectivity of the two viruses. There appears to be no seasonal incidence.

The spread of alastrim is brought about by intimate contact and overcrowding.

Ætiology.—Alastrim is very infectious to man, and attacks both sexes: no racial immunity has been observed. Guarnieri bodies have been described from the lesions (see p. 392). The virus is infective under experimental conditions for monkeys and calves, and produces lesions when inoculated into the cornea of rabbits. The crusts off the pocks are believed to convey the virus of the disease. The infectious agent probably resides in the nasal and buccal secretions at an early stage. Vaccination protects against alastrim in a very high degree. This, and the fact that two attacks may occur in the same individual, are common both to alastrim and to smallpox.

Pathology.—The lesions are present on the buccal mucous membrane as well as on the skin, and may extend from the palate down the trachea into the bronchi. The actual pocks appear to involve the skin tissues to a degree intermediate between those of chickenpox and smallpox; they rarely leave any scarring.

Symptoms.—The incubation period averages about fourteen days; prodromal symptoms may or may not be present. When observed, they are those of an influenza headache, with generalized aches and pains. Severe headache, vomiting, and rigors, typical of the onset of smallpox, are rarely noted. The eruption commences usually on the third or fourth day, but in some cases there is a complete intermission of all symptoms, during which the patient may return to his duties under the impression that he has recovered from an attack of influenza; after the lapse of the quiescent period the eruption appears first on the face and palate, then on the hands and arms, and later on the lower extremities. Thus, in these cases there is a prodromal period of seven or eight days.

Individual lesions.—The papules can be palpated under the skin, even before they are visible. As a rule, the eruption appears in one crop, and

closely resembles that of smallpox in every respect, any differences being due to the more superficial situation of the pathological process in the skin. The pock may be umbilicated, but collapses more completely on being punctured than does the smallpox vesicle, that is to say, it is less definitely multilocular. Drying or crusting begins at about the end of the first week, and crusts have usually fallen by the end of the second or third, at which period the patient is considered to be free from infection.

The rash naturally differs somewhat in appearance on a dark skin; the individual pustules, when ripe and full of pus, show as light creamy-coloured areas, in contrast to the dark purple of the surrounding inflamma-

tory zone, and appear like pearls upon a dark background.

Distribution of the eruption.—This is identical with the distribution of the smallpox eruption, which is centrifugal, and it serves to distinguish alastrim from chickenpox, the rash of which has a centripetal distribution. As in smallpox, the most protected parts of the skin are most free from eruptions, i.e. axillæ, groins, and abdomen. The parts most affected are the face, scalp, shoulder, back, arms and legs. Any part which has been previously specially exposed to irritation is more profusely affected; thus, pocks are apt to cluster at the site of old burns or scars.

Confluent rashes may occur but, though the appearance of the patient is somewhat alarming, his general health appears to be but little disturbed.

These cases may be associated with a considerable fever.

It has been noted by most writers on this subject that the fetor accompanying the rash of true smallpox is not present in alastrim.

Prodromal rashes are absent.

The mortality-rate is minimal; in the series recorded it is about 0.45 per cent. (Ribas and Moody).

Chickenpox may sometimes be severe in the tropics, owing to secondary bacterial infection. It should then be treated with penicillin or sulphonamides. It is far more commonly an adult than a childhood disease in tropical Africa.

Treatment is symptomatic only; patients should be isolated in a small-pox hospital or elsewhere.

Prophylaxis.—Vaccination offers the most efficient method of protection against this disease, as in smallpox. In spite of the mildness of alastrim, it is considered desirable at present to treat it as a form of smallpox, and not only to isolate patients but to vaccinate contacts.

TABLE V

DIFFERENTIAL TABLE

Smallpox

- Rash most abundant on face and back, scanty on abdomen and chest.
- (2) More abundant on shoulders than on loins.
- (3) The rash found on limbs, generally on arms and is centrifugal.
- (4) Favours prominences and surfaces exposed to irritation.
- (5) Lesions deep-seated with infiltrated base, circular in outline, homogeneous in character, multilocular and indented.
- (6) Spots all appear together and are therefore at the same stage.

Chickenpox

- (1) Abdomen and chest covered as thickly as face. Abdomen and back covered.
- (2) Distribution indifferent.
- (3) Rash tends to avoid limbs: centripetal.
- (4) Behaves indifferently.
- (5) Lesions superficial and base not infiltrated. Lesions frequently have an irregular outline, are not homogeneous, and generally unilocular. Never indented.
- (6) Crops of spots appear so that lesions are at different stages.

Subsection F.-FEVERS DUE TO ATMOSPHERIC CAUSES

CHAPTER XXV

HEAT-HYPERPYREXIA, HEAT-EXHAUSTION AND SUN-STROKE

Preliminary.—In hard muscular work the heat production is great and, even when well trained, a man does not turn more than one-third of the energy generated into work, two-thirds being converted into heat. An ill-trained man, on the other hand, has an efficiency no higher than a steam-engine, and converts 10–15 per cent. of food energy into mechanical work and wastes the remainder in the form of heat. Sweat cools the body by evaporation; the latent heat of evaporation is the chief factor concerned.

Marsh (1930) found in experiments on man that complete saturation with water vapour, if the surrounding air is at a temperature of 90° F., causes an immediate and uncontrollable rise of body-temperature. Pembry (1926) recorded the case of a man born without sweat-glands but otherwise healthy: owing to abnormal rise in his temperature he was unable to do muscular work in summer in England, unless his shirt had previously been soaked in water. People with ichthyosis are well-known to be intolerant of tropical temperatures, and a normal man treated with atropine in therapeutic doses is easily reduced to the same condition as one born without sweat-glands. Fatigue of the sweat-glands (Haldane) may be due to the low concentration of salt in the blood. A normal man of 60 kilos holds in his body no less than 40 kilos of water, of which about four are in the blood, and if water is slowly abstracted, it is replaced almost at once from the tissues. Men living in the Persian Gulf Littoral are exposed to a high atmospheric temperature varying between 125° F. and a minimum of 85° F. Hence, the European has to sweat continuously to keep his skin temperature at such a level that the circulating blood can be sufficiently cooled. Under these conditions diversis is so reduced that urine is passed perhaps only once a day.

The agent responsible for the phenomena of heat-stroke and heat-exhaustion is, of course, heat. Haldane originally demonstrated the importance of moist heat, that the wet-bulb thermometer was the most reliable guide, and that the limits of man's power of accommodation were passed when the temperature of still air

(as shown by the wet-bulb) exceeded 90° F.

Moist heat is therefore the most important factor, while the air temperature, wind velocity, and relative humidity are all of importance. In calm air the normal human body can support an air-temperature of 100° F., if the relative humidity is less than 90 per cent.; 120° F. if less than 40 per cent.; and 140° F. if less than 15 per cent. Rogers found that the mortality of patients with a temperature of 107° F. was 8·3 per cent.; with a temperature of 107° to 109° F. it was 29·2 per cent., and with a temperature of over 109° it was 69·2 per cent.

It is a matter of common observation that illness due to exposure to heat, in the absence of sunlight, is common amongst workers in deep mines, and stokers in the stokehold of steamships. On the other hand, the blue-violet rays in sunshine have a noxious effect on patients suffering from pellagra or smallpox, and cause photophthalmia and some blindness.

A certain amount can be learned from the effects of high environmental temperatures upon animals occupying different levels in the biological scale. Thus, frogs suffer from "heat-stroke" when the temperature of the water rises to 104° F.; it has been found that the lactic acid concentration in the blood and muscles of this amphibian rises to such a height that it becomes completely paralysed. Guinea-pigs begin to succumb to heat-stroke when the shade temperature rises to 110° F., rabbits when it reaches 116° F., and man at 130° F. In such circumstances the body is exposed to heat of such intensity that the natural powers of cooling are overwhelmed, the body temperature rises, increasing the respiratory and nitrogenous exchange, causing not only retention of heat but also overproduction.

Martin showed that the tropical sun can produce local heating of the skull to a depth of one to two centimetres of the skull surface, hair and tissues.

Acclimatization to hot conditions consists largely in training the sweat glands to function efficiently. Equally important is the redistribution of blood by the training of the circulatory system, whilst increase in plasma volume has also been shown to occur. The loss of solids in sweat causes cramps and loss of salts (Brunt).

An exceptionally exhaustive review of man's protection against the rays of the sun has been given by Critchly (1947). It is apparent that modern conceptions of the ill-effects of insolation have caused changes in former beliefs. The bogey of sun-stroke has been laid. According to the review of the physiological effects of sunlight by Blum (1945), a white skin reflects 45 per cent. of sunlight as compared with 16 per cent. by a black skin. This means that, though the negro's integument is less sensitive to solar radiation, absorption of heat is greater. Wartime experience has brought several changes into prominence. The over-clothing of the last century has now given way to a cult of nakedness and the vaunted health-giving effects of sun-tanned nudity are difficult to demonstrate, except that it definitely reduces the incidence of prickly heat, secondary skin infections and fungus disorders. The wearing of tinted glasses, especially of the polaroid variety, does protect the retina against tropical glare, whilst the artificial protection of the unshaded skin against the sun's rays shows that oils, fatty and greasy media do more harm than good for there is a tendency for the skin to become "fried." On the other hand preparations containing tannin are of greater service as a certain degree of keratinization is produced and benefit follows the use of pigmented washes containing flavine and permanganate of potash.

Heat-exhaustion may occur in any climate, high atmospheric temperature being the essential factor. Heat-hyperpyrexia has a peculiar endemicity.

It has been customary in previous editions of this book to classify the effects of heat into *Heat-exhaustion* and *Heat-hyperpyrexia*, but this attitude now has been modified to some extent by recent work.

Heat-exhaustion.—Ladell, Waterlow and Hudson have obtained physiological and clinical data on soldiers serving in Iraq as well as on patients in hospital. All men lose weight in hot weather, and the greatest loss takes place in those with the highest chloride sweat concentration. The evidence was based on low urine output in spite of high water intake, low urinary chloride output (less than 2 grm.) and raised blood urea. No

change occurs in the hæmoglobin or in the blood and plasma chlorides. Blood pressure falls as the weather grows hotter, but without evidence of cardiovascular inefficiency. Two types of heat-exhaustion are designated

types I and II.

Type I.—Cases are met in the first half of the summer in a hot humid climate. Prodromata are observed from 2-4 days, giddiness, vomiting and cramps are common in legs, thighs, arms, abdomen, hands and feet. The patients are pale, collapsed into profuse sweat. Fall in blood pressure is constant so that syncope occurs on standing. The urine volume is low with high specific gravity. Chemically it represents a salt deficiency dehydration. Plasma and blood chlorides are diminished with hæmoglobin and plasma protein raised, high blood urea, with extracellular fluid and plasma volume diminished. Prevention consists of increasing the salt intake (28 grm. daily). Fluid up to 16 pints a day should be drunk. Any man who is constantly losing weight and excreting concentrated urine with low or absent chloride should be regarded as a potential victim. In extreme cases intravenous injection of saline is followed by good results.

Type II (Thermogenic anhidrosis) is seen only in the second half of the summer in those who have come through the hottest weather without mishap. It is a fatigue phenomenon. Prodromata include cessation of

sweat for 1-8 days. There is dizziness, dyspnœa and anorexia.

Frequency of micturition often heralds the cessation of sweating. The skin is usually severely affected by prickly heat in the healing and disquamating stage. Vomiting, cramps and cardiovascular abnormalities are absent. Chemically these men are salt-deficient, but not to such an extent as in type I and they are not dehydrated. During convalescence sweat is secreted with a high chloride concentration.

The clinical picture here suggests a breakdown of the defence mechanism of the body against heat. The urine volume is larger and of low specific gravity. The salt concentration is normal, but urea is reduced. The incidence of this type can be reduced, if those who suffer from severe prickly heat can be given a break of a few days in a cool climate after

two months' continuous exposure to desert conditions.

Heat cramps are a frequent accompaniment of heat exhaustion and are common in hot countries. These cramps come on abruptly and are brought about by exercise. There is always a reduction in the chloride content of the blood plasma as was found by the Medical Research team in the Second World War. Ladell himself was particularly susceptible. When they are produced by exercise in the heat, muscle action currents showed definite changes and were enough to confirm the subjective complaint of cramp. Although cramps followed usually contraction of muscle, they could be excited by faradic stimulation. Two main factors appear to be involved in the causation—intracellular overhydration and chloride loss either absolute or relative. On the other hand general overhydration does not necessarily produce cramps (Ladell, 1949).

Mammillaria is a skin lesion associated with anhidrotic heat exhaustion. The affected skin is studded with pale firm elevations which are roughly circular and about 1 mm. in diameter. They bear no constant relation to hair follicles or the openings of sweat ducts. They are pale and appear to

contain less blood and less melanin than the surrounding skin. The affected skin feels rough like the studs of a nutmeg grater. *Mammillaria* is uniformly distributed from below the level of the neck over the anterior, posterior, and lateral aspects of the trunk (but not on the axilla), far down as the waist over the lateral aspects of the upper arms. After exposure to heat or physical exertion each lesion becomes more prominent both to the eye and to palpation.

Mammillaria may persist for varying lengths of time and restoration of the skin to normal is a slow process. It has been seen to last four months. Mammillaria has of course to be distinguished from "gooseflesh" in which the elevations form the centre of the hair follicles. A high sweat pH approaching neutrality and a high skin temperature are found only in anhidrotic heat exhaustion. There is also usually a delay in diuresis and a prolongation of the antidiuretic action of pitressin.

Mammillaria never develops without a history of preceding prickly heat in the humid climate of Karachi, although in the hotter and drier climates

mammilaria may not follow prickly heat.

O'Brien stated it was possible to restore sweating of a dry area of mammillaria by the topical application of anhydrous lanoline which is called "lipoid response." Application of fat to the skin prevents the evaporation of sweat. In other words inapparent perspiration is rendered visible. Probably this is due to a generalized increase in permeability of the keratin layer as a whole (Home and Mole, 1951).

HEAT-HYPERPYREXIA

Synonyms. Heat-stroke; insolation; thermic fever; siriasis; sun-stroke.

Geographical distribution.—Heat-hyperpyrexia appears to be remarkably restricted. Although this type has been reported in many countries, on careful investigation it will be found that a large proportion of the reputed cases are really other diseases, more especially cerebro-spinal fever, apoplexy, tuberculous meningitis, alcoholism, cerebral malaria, or some other phase of acute disease, but

not true heat-hyperpyrexia.

The endemic areas are:—in America, the east coast littoral of the United States, more especially in the great towns, the Mississippi valley, the coast of the Gulf of Mexico, the valleys of the Amazon and of the La Plata, and the South Atlantic coast; in Africa, the valley of the Nile, the coasts of the Red Sea, and a low-lying part of Algeria near Biskra; in Asia, Syria, Iraq, the valleys of the Indus and Ganges, South Persia, Lower Burma, Tonquin, and South-East China; in Australia, the Murray River district, the Queensland coast, and possibly the plains of Sydney. It is not met on the high seas, although it is well known on ships in the narrow, landlocked Red Sea and the Persian Gulf. During the 1914—18 war dangerous cases occurred most numerously in Iraq, especially during July, 1917, when for three days the temperature reached 122° F. in the shade, and 135° F. in the interior of double fly-tents.

Ætiology.—New-comers to the endemic areas and Europeans are more liable than natives or residents of long standing, and men over forty than those younger. All ages and both sexes are susceptible; but in consequence of their habits and more frequent exposure to the predisposing and immediate causes, men are more liable than women.

Heat-hyperpyrexia is generally attributed to direct action of atmospheric or solar heat on the body. Many theories of the modus operandi of this cause have been advanced. Among these may be mentioned superheating of the blood by the high temperature of the surrounding atmosphere. Hearne pointed out that heat-hyperpyrexia is associated with suppression of sweat, which may precede the onset of serious symptoms by 48 hours, for after prolonged exposure to high temperatures the sweat apparatus becomes exhausted and the glands cease to function. Coma, delirium and convulsions appear directly the body-temperature reaches 108° F. Hypodermic injections of atropine have been shown to predispose to heat-hyperpyrexia through its action upon the sweat-glands. The cramps are attributed to the coagulation of myosin in the affected muscles (Cajamian).

Blood chemistry.—Marked dehydration is associated with hæmoconcentration with an increase of hæmoglobin, sometimes to 110 per cent, and a corresponding increase in the red blood-cells. The leucocyte count is also slightly increased. There is a diminution of the blood chl orides and plasma bicarbonate, but a rise in lactic acid, blood-sugar and, usually,

blood-urea (Marsh).

The earliest sign of hypochloræmia is low, or absent. urinary chlorides. The test is performed as follows:—To 10 drops of a 24-hour specimen of urine is added one drop of 20 per cent. potassium chromate solution; this gives a canary yellow colour. Silver nitrate (2.9 per cent. solution) is added, drop by drop, until the colour changes suddenly to brown. The number of drops of silver nitrate equals the amount of sodium chloride, in grammes per litre. Sugar and acetone are occasionally found in the urine, and also a trace of albumin and a few hyaline casts.

Pathology.—The cause of death is usually circulatory failure. A notable feature of fatal hyperpyrexia is the early appearance of rigor mortis. The blood is remarkably fluid, or but feebly clotted. The venous system is loaded, dark fluid blood pouring from the phenomenally engorged lungs and other viscera on section. Both blood and muscles are said to yield an acid reaction, more or less pronounced. The red blood-corpuscles are crenated and do not form rouleaux. If the post-mortem examination is made shortly after death and before decomposition changes have set in, the heart in early rigor mortis, particularly the left ventricle, will be found remarkably rigid; this is sometimes described as being of "woodeny hardness." There may be some venous congestion of the meninges, and the brain shows small multiple hæmorrhages. On microscopic examination, necrotic changes in the ganglion cells, with chromatolysis of the nuclei, are found. The cerebro-spinal fluid is clear and under pressure. Cortical changes in the suprarenals have been described. In the lungs there is hæmorrhagic pulmonary edema. The intestinal mucosa, as well as that of the stomach, is swollen, and exhibits patches of congestion. The temperature of the cadaver continues to rise after death, and may reach 114° F.

Among prodromata of a major attack, which may show themselves with greater or less distinctness for an hour or two, or even for a day or two, are great disinclination for exertion, pains in the limbs, drowsiness, vertigo, headache, mental confusion, sighing, anorexia, thirst, intolerance of light—sometimes accompanied by chromatic aberrations of vision—suffused eyes, nausea and perhaps vomiting, præcordial anxiety, suppression of

sweat, urinary irritability, sometimes a sense of impending calamity, an

hysterical tendency to weep, and a quickened pulse.

Acute heat-stroke.—The first indication of anything seriously wrong may be a short stage of restlessness, or possibly of wild delirium. This brief preliminary stage rapidly culminates in coma and high fever, quickly passing into hyperpyrexia which may reach 112° F. The pupils are contracted, except immediately before death when, along with the other sphincters, they relax. The face is congested and the muscles rigid. The reflexes are partially or wholly in abeyance. There may also be, especially in the graver cases, free watery purging, the dejecta as well as the skin of the patient emitting a peculiar and distinctive mousy odour. The scanty urine may contain indican, blood-corpuscles, albumin and casts. The cerebro-spinal fluid is normal in appearance and its pressure slightly raised.

Willcox distinguished different clinical types of heat-hyperpyrexia:

(1) Gastric type.—A most deceptive form, in which the axillary temperature is normal, the rectal temperature raised, and gastric symptoms predominate, with congestion of the liver. Fatal hyperpyrexia may develop without previous warning.

(2) Choleraic type.—This form is sudden, with purging and general resemblance to true cholera; it may be fatal within three or four days.

The rectal temperature may rise to 110° F. after death.

(3) True heat-hyperpyrexia, in which nervous symptoms predominate, as described, accounts for 70 per cent. of the cases. The temperature may rise to 113° F. for a short time, and the patient yet recover (Marshall).

Unless active measures to lower temperature are taken early and vigorously carried out, in the great majority of instances, death will occur within a few hours, or even minutes, of the onset of insensibility. The immediate cause of death is generally the failure of respiration. Rarely do cases linger for a day or two. Partial recovery is sometimes followed by relapse. In favourable cases the disease usually terminates by crisis. Convalescence is rapid. Unless the patient is moved into different surroundings a relapse may occur; two or even three have been recorded.

The death-rate may be materially reduced by early and judicious treatment. In Iraq, during the 1914-18 war, the case-mortality among

British troops was about 8 per cent.

Diagnosis.—The high fever is sufficient to differentiate heat-hyper-pyrexia from sudden insensibility caused by uramia, by diabetic coma, by alcoholic and opium poisoning, and by all similar toxic conditions. Carbon monoxide and hydrogen sulphide poisoning must also be thought of. Cerebral hamorrhage, particularly pontine, may, after some hours, be followed by high temperature; but here the febrile condition follows the insensibility, whereas in heat-stroke the febrile condition precedes insensibility. Diagnosis from a cerebral malarial attack may be very difficult; chief reliance has to be placed on the history, if obtainable, on the condition of the spleen, and especially on the result of microscopic examination of the blood; but sometimes the subtertian parasites may

not be demonstrable for two or even four days from the onset. Malarial fevers and the early stages of the eruptive fevers in children are very apt to be regarded as heat-stroke, particularly if there has been recent exposure to a hot sun. Cerebro-spinal fever, so often mistaken for heat-hyperpyrexia, may be recognized by the occipital retraction, the irregular pupils, the frequent occurrence of strabismus, Kernig's sign, the comparatively low and fluctuating temperature, the associated herpes, the initial rigor, and its duration. Lumbar puncture will, of course, give a clear differentiation. The fluid is often under high pressure, but is clear in heat-hyperpyrexia, and lumbar puncture should be performed in these cases, not only for diagnosis, but as a therapeutic measure. Uncomplicated heat-stroke is accompanied by hypochloræmia, dehydration, absence of urinary chlorides, excess of lactic acid, and low content of bicarbonates in the blood.

Marsh states that during a heat-wave in the Persian Gulf mild cases of heat-exhaustion are usually in the majority, and so it is difficult, sometimes, to distinguish cases of pure fright from genuine cases. Real cramps constitute a valuable diagnostic sign. They are so extremely painful that the patient cannot sustain a conversation and the affected muscles can be felt

to contract forcibly.

Men of fifty years of age or over, or young men who have been suddenly introduced to a hot climate, should be carefully examined, for they may develop rapid hyperpyrexia without any of the usual premonitory signs. The correlation of heat deaths with increasing age is probably due to progressive diminution in the heart reserve.

Treatment.—Treatment must be instituted at the earliest possible moment. A few hours' delay may mean death to the patient. In all fulminating fevers, including heat-hyperpyrexia, in warm climates, if malaria be suspected, particularly if the subtertian parasite be discovered in the blood, quinine should be injected intravenously or intramuscularly at once (7-10 gr. of the dihydrochloride); this dose should be repeated three or four times at intervals of four hours. Should there be any suspicion of alcohol poisoning, the stomach should be washed out. every case of heat-stroke, whether it has been deemed advisable to administer quinine and other antimalaria drugs, or not, attempts must at once be made to reduce temperature by such rapidly acting measures as the cold bath, or ice applied in various ways to the head and body. The patient should be placed on a wet sheet supported upon bed cradles, thus forming a moist chamber in which he lies; the whole may rest upon a rush-covered bed or "angareeb." Mackintosh sheets must be avoided. The continuous water-spray with iced water, together with an electric fan, simulates the natural process of sweating to the best advantage. In the absence of electric fans an iced wet sheet may be wafted up and down over the patient's abdomen by a punkah-like arrangement. Rubbing the skin with ice, by constricting the capillaries, apparently only obstructs evaporation. A thermometer should be kept in the rectum and the application of cold should be discontinued as soon as the thermometer in the rectum has sunk from 106° to 102° F., or from 109° to 104° F. powerful antipyretic measures are carried beyond this point the fall of temperature may continue below the normal, even as low as 91° K., and

dangerous collapse ensue.

Fluid must be given in large quantities, as 0.25 per cent. saline drinks or, if the patient cannot swallow, as intravenous normal saline, of which quantities up to 20 pints may be given. The fluid and salt requirements are regulated by the appearances of dehydration, the blood concentration (estimated by red cell count and percentage of hæmoglobin), the amount of urine and the blood pressure. Intravenous saline is indicated if the systolic blood pressure is below 100. It must be given with great care, for the cardio-vascular system may be unable to deal with it. If the blood pressure does not rise, the patient may die of pulmonary cedema, which may occur after 9 pints has been administered.

A balance sheet of fluid intake and output should be kept, and fluid should be given in large quantities until the total output balances the total intake. In this balance sheet at least 8 pints must be allowed for

daily loss of fluid by the sweating of a man at rest.

On discontinuance of the iced sheet, the patient should be wrapped in a dry blanket; very likely, perspiration, a favourable sign, will then set in. Stimulants may now be necessary. Strychnine, owing to the marked tendency to convulsions in heat-stroke, must on no account be used as a cardiac stimulant; Chandler, as the result of his large experience, recommended the injection of 40 min. of tincture of digitalis. Convulsions are best controlled by cautious venesection. As death in heat-stroke generally results from failure of respiration, Hearne and others strongly recommended artificial respiration when the breathing threatens to become suspended; it should be maintained for half an hour or longer. Lumbar puncture is indicated as a rational method of relieving intracranial pressure. Gastric cases should receive a liberal supply of bicarbonate of soda—30 gr. every two hours. Diarrhœic and dysenteric cases are specially liable to hyperpyrexia because of loss of fluid. Nourishment is needed; sweetened diluted tinned milk may be used.

During convalescence great care must be exercised to shield the patient from all influences calculated to provoke relapse. The power of sweating may be in abeyance for three weeks or longer.

Sequelæ.—In some (McAlpine, 1946), mental confusion with incontinence, aphasia, pyramidal and cerebellar signs persist. As recovery proceeds the patient becomes more orientated, ceases to confabulate, and shows prognostic improvement in memory similar to that after a head injury, but in a small percentage a gross memory defect for recent and past events persists, accompanied by lack of interest, childish behaviour and incontinence. Inability to talk may be due to aphasia or gross dysarthria. Signs of unilateral or bilateral hemiplegia clear up, but the most constant sequel is a cerebellar picture which manifests itself in ataxia and rarely in nystagmus. Sometimes the picture of disseminated sclerosis is reproduced.

Prophylaxis.—Patients in hospital are especially liable to heat-hyperpyrexia. The most valuable practical method is to attempt to forestall it by periodically inspecting the patients to find out those with

commencing suppression of sweat, urinary irritability, restlessness and insomnia.

A heat-stroke hut, or treatment room, or even a heat-stroke ward, are

most desirable additions to hospital equipment in the tropics.

An improvised cooling apparatus can be made by filling the radiator of a lorry with ice and driving the fan-driven air by means of a tunnel

into a one-bedded bunk (Morton).

A special refrigerating apparatus consists of a horizontally placed ammonia compressor working in conjunction with a brine-circulating system. At Masjid-i-Suleiman in South Persia (Anglo-Iranian Oil Fields) heat-stroke cases and, indeed, all cases of fever, are kept in outlying stations during the heat of the day until the cool hours between midnight and five a.m., in a cold-storage chamber attached to the ice-plant. During the coolest part of the night they are put into a fast ambulance and taken to the nearest heat-stroke hut where they are kept until complete recovery has taken place. Such accommodation should be provided for 10 per cent. of the population exposed to risk, in order to provide for the rush of cases during a heat wave.

Buildings must be so constructed that they do not retain heat, and cool down quickly. The roof should be double, enclosing a wide air space, or it should be of thick thatch, projecting well and shading the upper walls. A ventilated verandah should extend all round, supporting hanging curtains of strong canvas, surfaced on both sides with aluminium foil. Double walls

should be provided.

Efficient methods of cooling the air are employed in industry in many parts of the world. These include methyl chloride, or ammonia refrigerating machines, or the cooling powers of evaporating water at atmospheric temperatures and in vacuo. Air-conditioning of houses and dwelling-rooms is commonly found in New York and other American cities, and the matter is solely one of expense.

The cost of maintaining a cool chamber is £400-£500 per annum.

The drink available for all workers in endemic areas of heat-stroke should consist of: sodium chloride 6 oz., potassium chloride 4 oz., water 1½ pints. Of this concentrated solution, 17 fluid ounces are added to 8 gallons of water for drinking; a flavouring may be added (Dunlop, McNee and Davidson).

As the result of these measures heat-stroke has been greatly reduced and

has almost ceased to count as a cause of invalidism.

Acclimatization.—Some organizations in the tropics endeavour to avoid the ill-effects of heat by ensuring fitness and acclimatization of the workers. In the Witwatersrand gold mines, candidates for employment are subjected to an exercise tolerance test in rooms artificially heated to 94° F., wet-bulb, and are then graded on their reactions, suitable candidates being put through a further course involving exposure to high temperatures in stages and lasting, sometimes, for fourteen days. Soldiers should be given lectures on the precautions necessary in hot climates.

Fewer casualties occur from heat among men born and bred in hot climates than among those reared in temperate climates. While there is a general agreement that excessive alcohol consumption is contra-indicated,

less attention has been paid to the profound effects that may arise from shortage of water and to the importance of replacing salt lost in sweat. The minimum daily fluid requirement in the hot season is 16 pints, and a man doing hard manual work may take 4 gallons. A daily ration of $\frac{3}{4}$ oz. of salt is essential, and should be taken for several days before entering a heat stroke area, and continued throughout residence there. There is no evidence that alcohol in moderation is harmful. Constipation in the hot season is almost physiological and must be avoided, but care should be taken that when saline purges are given, plenty of fluid is drunk, since a watery motion may induce dehydration, and a patient may be constipated because he is already somewhat dehydrated.

In the 1939-45 war it has been noted that, during the hot weather of 1942, nearly three-quarters of the cases of general effects of heat amongst troops in Persia and Iraq occurred before, during and after disembarkation. Many could have been prevented, had adequate precautions been taken on board ship. High atmospheric humidity with a wet bulb temperature of 83° F. is the danger point.

It is dangerous for persons who have suffered from heat-hyperpyrexia to return to the conditions or surroundings that brought it on in the first place.

Section II.—VITAMIN DEFICIENCY DISEASES (AVITAMINOSES)

CHAPTER XXVI

BERIBERI AND OTHER VITAMIN B, DEFICIENCIES

Synonyms.—Kakke; Barbiers; Polyneuritis Endemica.

Definition.—Beriberi is a form of multiple peripheral neuritis occurring endemically, or as an epidemic, in most tropical and sub-tropical climates. and also, under certain conditions, in more temperate latitudes. mortality may be considerable, usually from cardiac failure. Experiences of nutritional deficiencies during the 1939-45 war were considerable and the results appear to indicate that the boundaries between the different recognized vitamin deficiencies are not so clearly drawn as had been formerly thought, but on the whole the clinical picture of acute and chronic beriberi remains surprisingly uniform.

Geographical distribution. Until recently extensive, corresponding with tropical and subtropical belts. Formerly scourge of mines and plantations of Malaya, China and Indonesia; amongst coolie gangs on engineering works such as Panama Canal and Congo Railways; in Dutch army in Sumatra and in Japanese navy. A notable outbreak in prisoners in islands of Java Coast (Elshout and Lentjes) has been recorded. Still fairly common in ports and cities of Japan, in China, Philippines, India and Africa.

Epidemics have been reported in W. Australian aborigines and amongst Chinese in E. Australia.

Beriberi was once seen in a lunatic asylum in Dublin, as well as in institutions in U.S.A. and France; also in fishermen in Newfoundland and N. American coast, in Westman Islands, Iceland (1933), living on fish diet deficient in vitamin B1.

Epidemiology and endemiology.—Sex, age, occupation.—Beriberi attacks both sexes. It is not uncommon in the breast-fed infants of beriberic mothers. This form, called infantile beriberi, may declare itself in varying ways.

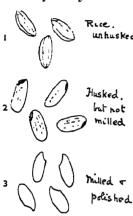
Ship beriberi.—Beriberi was prevalent among the native crews, more rarely, though occasionally, among the European officers and sailors, of

ships on the high seas.

From 1894 up to 1920, or thereabouts, the disease was common in European crews of Swedish and Norwegian ships, which were in far better sanitary condition than British ships, and yet beriberi was comparatively rare in the latter. modern explanation is that, since the year named, the crews of the Norwegian mercantile marine have been provided, under the terms of a statute, with bread baked from white flour, or a mixture of wheat and rye, so that their diet is inadequate in vitamins. Ship beriberi holds a place intermediate between true beriberi and scurvy, and is closely related to the disease found among the Rand miners of South Africa. A similar disease has recently been noted amongst the whale fishers of South Georgia. Stewart (1945) also observed the association of scurvy and polyneuritis and considered this was identical with so-called "ship beriberi." In Newfoundland beriberi of both forms is found at times when the diet is reduced to a regime of bread and molasses (Aykroyd). A number of cases have been reported from H.M. ships in the Persian Gulf.

Asylum beriberi.—The Dublin lunatic asylum, built for 1,000 inmates, had 1,500 crowded into it when beriberi broke out, due to dietetic causes.

Ætiology.—The earliest investigators of beriberi believed that it was a degenerative multiple neuritis indistinguishable from that produced by alcohol or diphtheria, and that it was due to an infection or intoxication, and much effort was directed to the discovery of the poison. All these are now a matter of history, for they have been replaced by the vitamin-deficiency theory.



54. — Showing various stages in milling the rice grain. 1, Rice grain in the natural condition enclosed in the husk or enclosing glumes; 2, After removal of the husk, but retaining the pericarp or "silverskin " and the embryo; 3, After milling and polishing; both "silverskin" and embryo are removed and the grains are " polished " by rubbing with talc between sheepskins. (After Chick and Hume, "Trans. Soc. Trop. Med. and Hyg.")

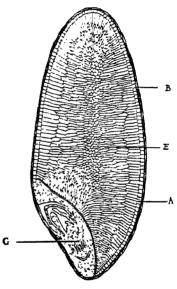


Fig. 55.—Diagram of longitudinal section through a grain of wheat showing (a) aleurone layer of cells forming the outermost layer of the endosperm, removed with the pericarp during milling; (b) pericarp forming the branny envelope; (e) parenchymatous cells of the endosperm; (g) embryo or germ. (By permission of H.M. Stationery Office, from Dr. J. M. Hamill's "Report on the Value of Bread made from Different Varieties of Wheat.")

If a fowl or pigeon be fed exclusively on "paddi," that is, rice from which the husk has not been removed, it will thrive and very likely gain weight; but if it be fed exclusively on a diet of white rice and grain, that is, rice from which the pericarp has been completely removed, after a short time, it will show signs of peripheral neuritis, lose weight and, if the exclusive diet be persisted in, die with all the signs of a multiple peripheral neuritis. This polyneuritis gallinarum (or p. columbarum)—as it is called—is evidently the result of the deprivation of some element of food essential for the proper nutrition of the nervous system of the bird, and the element is located in the pericarp and germ of the rice grain

after (Figs. 54, 55). Almost miraculous recoveries in the stricken birds take place hypodermic injection of an extract of the germ centre of wheat or other cereal.

The greater part of the rice grain is starch, and covering the central starch core there is a thin aleurone layer containing the proteid and fat constituents of the grain. Externally there is an adherent layer, the pericarp, which varies in colour from red to white according to the variety of the rice. The pericarp contains the salts. The grain itself is covered by a husk, which is discarded as chaff.

Conditions under which rice is grown.—Rice grows normally in puddled fields in which a layer of water is allowed to remain until the grain is almost ready for reaping, and this puddled rice has a nutritional value of approximately one-third less than the same rice grown under dry rain-fed conditions; it contains also a lower content of vitamin B_1 ; the Chinese eat mostly polished rice, normally obtaining their store of vitamin B_1 from fresh vegetables, shortage of which has from time to time led to a great increase of beriberi in Malaya.

Fraser and Stanton showed—and their observations have been abundantly confirmed—that the antineuritic element is located in the pericarp of the rice grain, in the aleurone layer, and in the embryo of the grain, that it is soluble in water and alcohol, is stable in acid but unstable in alkaline solutions, is thermolabile—being destroyed by a temperature of 130° C.—and that it is dialysable; that it is not a phytin or a fat, and that, although itself not containing phosphorus, the amount in any given rice is a reliable indication of the safety, or otherwise, of that rice as a staple article of food. Rice containing less than 0·4 per cent. of P_2O_5 they considered unsafe, and believed that its persistent use might lead to beriberi. B_1 was isolated by Jansen and Donath (1926) and synthesized by Williams (1936).

The polyneuritis of the fowl is identical clinically and ætiologically with the polyneuritis, called beriberi, occurring in man. For, as has been both accidentally and intentionally done, if the same experiment with rice-feeding be tried on man the result is identical—beriberi is induced. Thus, following the lines of the earlier experiments of Fletcher, Fraser and Stanton, Strong and Crowell conducted a series of experiments on twenty-four life-sentenced prisoners, and were able to prove (a) the non-communicability of the disease, and (b) its production in man solely by means of diet. A similar condition has been produced in rats.

Acting on these findings, the governments of Singapore and the Federated Malay States forbade the use of white or polished rice in their jails, lunatic asylums, schools and hospitals, with the result that beriberi, which until then had been the cause of an enormous mortality and morbidity, has been practically banished. Corresponding results have accrued from the same practice in Indonesia, the Philippines, and elsewhere. In India decorticated rice is practically the staple diet of many millions, though beriberi is endemic only in a few circumscribed areas in Bengal and Assam, the north-east coast of Madras, the coast of Burma, and certain river valleys. The basal factor in India must be a fundamentally poor diet, whether of rice or other food grains. The period of development of beriberi in man was determined by Fraser and Stanton as between eighty and ninety days. The part that vitamin B, plays in beriberi has now become clearer. Walshe (1941) claimed that, both clinically and pathologically, beriberi is a typical polyneuritis, differing in no essential from other varieties. The nervous signs and symptoms are those of a multiple symmetrical nervous lesion, the cardiac manifestations also those of polyneuritis.

Vitamin B_1 (aneurin: thiamin).—Vitamin B_1 is composed of pyrimidine and thiazole nuclei. It is 2-methyl-5-(4-methyl-5- β -hydroxethyl-thiazolium chloride) methyl-6-amino-pyrimidine hydrochloride ($C_{12}H_{17}ON_3S$), a colourless water-soluble crystalline substance containing a molecule of water of crystallization and melting at 248–250° C. In dry conditions it is stable at 100° C. for

twenty-four hours. The rate of destruction is increased by presence of water and alkali. It is oxidized to thiochrome by potassium ferricyanide in the presence of alkali.

Destruction in ordinary cooking processes is not very great, if soda be not added to vegetables. Pressure cooking, even when rapid, causes considerable destruction. The destructive action of sulphites is of some importance, since these are used in the preservation of fruit pulp and juices, and depends on the pH of the medium. Vitamin B_1 is destroyed on autoclaving and largely inactivated when yeast and liver are subjected to heat under pressure. When subject to mild oxidization with potassium ferricyanide, the alkaline solution is converted to thiochrome which exhibits intense blue fluorescence under ultra-violet light, a reaction employed in the estimation of B_1 . Thiochrome is devoid of any vitamin-like action.

B₁ is widely distributed in raw foodstuffs, the richest sources being whole cereals, especially the pericarp and <u>germ</u> (see p. 409), <u>yeast</u>, pork and <u>pulses</u>. Vegetables, including <u>potatoes</u>, are an in<u>portant source</u>. The diet of the working classes in Britain is so <u>deficient in B, that</u> white could with advantage be replaced by wholemeal bread. <u>Yeast</u> is an exceptionally potent source and should be used as a dietary supplement when large quantities are required. Milk is a poor source.

The physiology of B_1 .—The original suggestion of Funk that B_1 plays some part in carbohydrate metabolism has been substantiated. Two of the intermediate products of the metabolism are lactic and pyruvic acids. Glucose is not directly oxidized in the body, but is transformed into carbon dioxide and water in a number of stages during which lactic and pyruvic acids are produced. B_1 deficiency in animals results in incomplete metabolism and is associated with increased urinary excretion of lactic acid. The blood level of lactic acid appears to be abnormally high in beriberi patients.

Pharmacological action.—Subcutaneous injections of from 50-500 mgm. per kilo cause an increased oxygen intake of 20 per cent. in guinea-pigs within half an hour. B₁ also produces diuresis which is thought to be of central origin, whilst toxic effect occurs only when very large doses are given. Man will tolerate intravenous injections of 500 mgm. daily for one month. Because of the great difference between therapeutic and toxic doses and lack of cumulative toxicity, B₁ can be regarded as a particularly safe therapeutic agent for prolonged use.

Cowgill (1939) proved that man is unable to synthesize B_1 , or store it to any appreciable extent. In experimental animals signs of deficiency may be produced in a period of 10 days to 3—4 weeks, but symptoms in man may appear after a few weeks of inadequate diet. It is readily absorbed from the small, and possibly also from the large, intestine but, even when ingested in sufficient quantities, it may escape absorption in certain digestive disturbances, such as comiting and diarrhœa, or destruction of intestinal mucosa (chronic bacillary dysentery, ulcerative colitis). Diseases associated with diuresis may wash considerable quantities of B_1 from the tissues before it can be utilized. Absorption occurs by simple diffusion.

The larger part of B_1 is stored in the liver, kidneys and muscles, and it is abundant in the normal heart. Depletion occurs most rapidly in the muscles and is slowest in the brain. B_1 is excreted in the urine, and the kidney concentrates it from the plasma to a marked degree, perhaps twenty times or more, but it appears that only a small proportion of the vitamin given by the mouth, or by injection, is excreted in the urine, the rest being destroyed in the body. It is also excreted in the milk but no appreciable quantity in the fæces. Harris and Leong (1936) believed that excretion of less than 12 I.U. (see p. 412) per day

in the urine is evidence of B, deficiency.

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Human requirements.—An increase in metabolic rate increases B₁ requirements, Thus, beriberi is more prevalent amongst stokers than sailors, owing to their greater physical exertions. Similarly, males suffer more from beriberi than non-pregnant women, due to harder physical work. In Manila there is a high incidence of beriberi among pregnant and nursing mothers. As the metabolic rate rises during fever there is apt to be an association of beriberi with malaria and other pyrexias.

The International Unit is the antineuritic activity of 3γ of pure B_1 (i.e. 333 I.U. = 1 mgm.). The minimum daily B_1 requirement in international units is expressed in Cowgill's formula: daily calorie intake 0·0284 × weight in kilos × 0·05. Therefore, for an adult of 70 kg. (11 st.) on 3,000 calories a day the minimum requirement would be approximately 300 I.U. or 1 mgm. The figure is the physiological minimum, but 500–700 I.U. (1·75 mgm.) is the desirable intake. The metabolic rates in pregnancy, lactation, infancy and childhood, per unit of body surface, are greater than in normal adult life; therefore a greater B_1 requirement is necessary. Infants require approximately 50–60 I.U. (0·2 mgm.). Up to adolescence the B_1 requirements increase with age. In hyperthyroidism and during exercise the B_1 requirements are increased.

It is, however, clear that deprivation of B₁ alone is not sufficient to cause beriberi in fowls or man, for patients dying of anorexia nervosa do not develop polyneuritis. The significance of B₁ is in relation to carbohydrate metabolism, rather than to its direct effect on the nervous system. Human and avian nervous systems can be deprived of B1 with impunity when no carbohydrates are given. B, acts as a catalyst in carbohydrate metabolism of the nerve cell and heart muscle. In the absence of B₁, cellular carbohydrate metabolism breaks down at the stage of pyruvic-acid formation. This substance accumulates in the cells, where its presence can be detected. It is, however, an error to suppose that pyruvic acid is toxic. Peters and his colleagues believe that B, functions as a co-enzyme in the metabolism of carbohydrates and plays a part in the oxidation breakdown of pyruvic acid. Therefore accumulation of this acid or of pyruvates in the blood and central nervous system, and its excess in the urine, is related to the deficiency of B1. It is therefore essential for normal growth and the maintenance of body weight.

Incidence.—The incidence of beriberi is greatest in those regions where polished rice and refined cereals form the bulk of the diet. It constitutes one of the most potent causes of mortality in Japanese infants. From 1920–1929 there was an average of 17,000 deaths from this cause in Japan. Beriberi appeared in the beleaguered troops at the siege of Kut in 1916. Balfour stated that every pregnant woman in S. India suffers from it. In S. China beriberi is common in the later months of pregnancy and in the puerperium.

In people living on an inadequate diet the raised basal metabolic rate resulting from fever increases the liability to beriberi—as after smallpox, cholera or meningitis. In China, for instance, 10 per cent. of patients show some reflex abnormality suggesting latent beriberi. Thus, any lowering of the general resistance leads to the development of polyneuritis. Breast-fed babies born of mothers suffering from the disease are themselves liable to it.

Pathology.—The post-mortem appearances of beriberi resemble the accepted descriptions of peripheral neuritis. There is a degeneration of the peripheral

nerves—more especially of their distal ends—and there is secondary atrophic degeneration of muscle, including that of the heart. Degenerative nervechanges may be detected in the nerve-centres and throughout the implicated neurones, as in other forms of peripheral neuritis. There is invariably an involvement of the vagus with degenerative changes in its root in the floor of the fourth ventricle. Microscopically, the nerve-trunks show changes, from a slight

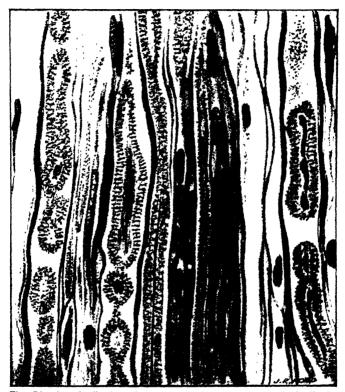


Fig. 56.—Longitudinal section of external popliteal nerve in beriberi.

One medullated fibre in centre is practically intact; the others show typical fragmentation of myelin sheath with swelling of remains of nerve-fibre.

(From a preparation by Dr. A. C. Stevenson.)

medullary degeneration to complete destruction of the nerve (Wallerian degeneration). Regenerative processes occur side by side with the degenerative (Fig. 56). As a rule, some fibres in the vagus and sympathetic escape; thus, the cardiac branches in the heart-muscle and the bronchial and cooplageal twigs are usually unaffected. According to Vedder, the membranes of the spinal cord are often congested and cedematous; scattered fibres in all tracts show the same kind of changes as the peripheral nerves. Degenerative changes are also found in the anterior and posterior horn cells, as well as in the sympathetic ganglia. If there is anything peculiar about the post-mortem appearances in beriberi, it arises from the somewhat special implication of the central and peripheral organs of the circulation—namely, dilatation of the heart, especially of the right side, and great

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accumulation of blood in the right heart and in the veins. In addition, there is a marked liability in many cases to serous effusion into the pericardium, pleural cavities, peritoneum, and cellular tissue. This very marked liability to serous effusion and the tendency to cardiac dilatation may be said to be more or less of the cardiac muscle naturally interferes with the normal fluid exchange within the fibres and therefore with its contractibility. According to Mebius. when vitamin B, is deficient, full muscular contractibility is impossible owing to waterabsorption (hydropic degeneration of Wenckebach). The average weight of the Japanese heart in beriberi is 368 grm. (normal 300 grm.). The enlargement is particularly noticeable on the right side, especially the right auricle, and the walls are paper thin. Without doubt, water retention in beriberi is of the greatest importance in elucidating the mechanism of symptom production. Œdema of the lungs also is not uncommon, and has, probably, a pathology similar to that of the connective-tissue cedema. There is no nephritis, but pressure congestion of the liver (nutmeg liver). Duodenitis is frequent.

The general affection of the whole nervous system, involving the central and peripheral structures, is identical with that found in diphtheritic or alcoholic

neuritis.

General considerations.—As beriberi of various types was so extremely common in prison camps in the Far East from 1942 to 1945 it has been the subject of many outstanding clinical studies conducted on scientific lines under conditions of the greatest difficulty by devoted medical staffs. The calculated value of the rations was deficient in all factors, except vitamin C. carotene and iron. On such a low diet it took 80-100 days for the development of the beriberi syndrome. The epidemics were controlled by prophylactic vitamin B1. The critical value for the B₁-carbohydrate ratio was in the region of 0.4 mgm. per 1,000 carbohydrate calories. In the camps the change from European to Asiatic type of diet, and the prevalence of diarrhœa and dysentery, reduced bacterial synthesis to a minimum. Multiple deficiencies of other factors were present and consequently the borderline between beriberi and pellagra became very narrow. According to Shillane, on the whole, as compared with pellagra, the clinical evidence of multiple deficiencies in beriberi did not occur in such profusion or variety.

Symptoms. Primary Beriberi (Naturally-occurring disease).—Beriberi assumes varying clinical forms according to the extent and position of the nervous lesions. It is insidious in onset, but it may occasionally be ushered in by acute symptoms ending fatally within a few hours without development of any symptoms referable to the nervous system. As a general rule, it is classified into two main forms, according as the peripheral nerves or the cardiovascular system are most affected. The former is known as paraplegic or "dry" beriberi, the latter as cedematous or "wet" beriberi. It must be understood that in all its forms beriberi is the same disease, and that a clinical classification has but a conventional value. Sudden death from heart failure may ensue, especially in cedematous cases.

Paraplegic beriberi (Fig. 57).—There is a certain amount of anæsthesia or numbness of the skin, particularly over the front of the tibiæ, the dorsa of the feet, the sides of the thighs, perhaps also of the finger-tips, and one

or two areas on the arms and the trunk. Deep sensibility (Abadie's sign), elicited by compression of the Achilles tendon, is usually numbed or entirely lost. The calves may be strikingly thin, the gastrocnemii flabby, and if they and the neighbouring muscles are handled somewhat roughly, particularly if they are squeezed against the underlying bones, the patient will call out in pain and try to drag the limb away. Toe and foot-drop can frequently be demonstrated. Weakness spreads upwards, first involving the extensor muscles of the leg, and then the extensors and flexors of the thigh. The skin of the limbs becomes shiny. The thenar, hypothenar,



Fig. 57.—Ataxic or paraplegic beriberi, showing characteristic attitude.

plantar and arm muscles, like the calf muscles, may be wasted, flabby and exhibit fibrillary twitchings. Very probably there is a loss of fat, the panniculus adiposus being everywhere meagre. If tested electrically, the muscles exhibit the reaction of degeneration. If the knee reflex be tested in the usual way, it is at first increased, but after the first week there will be no response whatever; nor can any clonus be elicited, but occasionally a reflex contraction of the hamstrings may take place, giving a false impression of a knee-jerk. As a rule, all the deep reflexes are lost; but the superficial, unless in extreme paresis and muscular atrophy, are usually present and more or less active. If, in severe cases, the patient is set to button his jacket or to pick up a pin, possibly he has a difficulty about it.

or perhaps he cannot; he may bungle and fumble like the advanced ataxic. The fibres of the affected muscles, when struck with a patellar hammer, often contract locally in a particularly painful manner known as mycedema.

There may be wrist-drop (Fig. 58).

There is more than ataxia, however, for the hand-grasp is so enfeebled that the patient may have a difficulty in holding his rice-bowl as well as in feeding himself. There is no tremor of the hands; and never, or very rarely, is there any paresis of the ocular muscles, or of the muscles of the face, of mastication, of the tongue, or of the pharynx. The sphincters



Fig. 58.—Paraplegic beriberi, showing wasting of extensor muscles and wrist-drop.

and bladder operate satisfactorily, and the functions of the alimentary canal are carried on fairly well, although there is often some dyspeptic distension and oppression after food. If the patient can walk at all, his gait will be markedly ataxic; but, in addition to want of co-ordinating power, there is great muscular weakness. If he is laid on the bed and asked to raise his legs, he is perhaps hardly able to get them off the mat, to cross them, or to place one foot on top of the other. Very probably he is the subject of marked foot-drop, so that he drags his toes when he attempts, in walking, to advance the foot; he has therefore to raise the foot very high, letting it fall on the ground with a flop when he brings it down again (steppage gait). His ataxia and his muscular weakness, as well as the partial anæsthesia from which he suffers, force him to adopt a

variety of devices to assist him in progression. Although mental symptoms are uncommon, defects of memory often occur.

The general health is good, for the most part; the tongue is clean, the bowels are fairly regular, there is no fever. Loss of sphineteric control does not occur until very late. Digestion, assimilation, and excretion are satisfactory.

Dean Smith has recorded that in prison-camp dry beriberi no association with any detectable cardiac abnormality was ever observed.

Cardiac beriberi, wet beriberi. -Instead of being wasted, as in paraplegic cases, the face is puffy and heavy: the lips possibly slightly cyanosed; and the arms, hands, trunk, legs, and feet are distended with œdema (Fig. 59). It may be thought at first from the cedema that it is a case of acute nephritis, but an examination of the scanty, dark-coloured urine shows that it is of high specific gravity and contains no albumin, or only a mere trace. Careful observation will discover that the ædema is somewhat firmer than that of nephritis and, in not a few instances, that it does not involve the scrotum. Occasionally it is peculiarly localized and fugitive. A bruit and other evidences of dilatation of the heart are discovered; Occasionally irregularity may be associated with slowing of the heart-beat, and heartblock may occur in such cases. The liver is frequently swollen

Fig. 59.—Gedematous beriberi with paresis of legs in Gold Coast native boy. (Dr. S. A. Maclean.)

and tender. The lungs may (or may not) present signs of single or double hydrothorax, but they themselves are healthy. The patient can hardly walk—partly from breathlessness, partly on account of mechanical interference by the dropsy with the movements of the legs, partly, perhaps, from some degree of paresis. He may have ankle-drop; if firm pressure be brought to bear on the calf-muscles through the cedema, signs

of hyperæsthesia of the muscles may or may not be elicited. Knee-jerks are generally absent, and there is numbness of the shins and finger-tips. The tongue is clean, the appetite fair, and there is no fever. But there may be præcordial distress and even pain, and, as this is aggravated by a full meal, the patient eats sparingly. The amount of urine is generally very much reduced—even to a few ounces.

In this patient, therefore, there are the same signs of peripheral neuritis and of dilatation of the heart as in the other cases. In addition, there is a somewhat firm edema, which is not altogether cardiac, but, as its character and the circumstances in which it is found suggest, is probably connected with the play of transudation and absorption in the connective tissues.

Dean Smith (1947) found in Japanese prison camps that multiple deficiencies of other factors were present in the majority of fatal cases. Most patients increased in weight as much as 15 lb. in a week, which they

lost with great rapidity directly diuresis occurred.

When the heart is examined, if the case be at all recent or moderately severe, the impulse is diffuse; there is epigastric pulsation; the carotids throb violently; and there is that peculiar wobbling, pulsating movement in the jugulars that denotes tricuspid insufficiency. "Pistol shot" sounds are heard on auscultation over the larger arteries. On percussion the præcordial area is frequently enlarged, perhaps very greatly enlarged. especially to the right; and on auscultation loud bruits, usually systolic in rhythm, may be heard. Marked reduplication of the sounds, particularly of the second, is noted. The auscultator may be impressed, in a large proportion of cases, by the peculiar spacing of the intervals between the sounds. It may be hardly possible to tell by the ear alone which is the first pause and which is the second. They seem alike in point of duration (tic-tac rhythm); so that the sounds resemble the beats of a well-hune pendulum clock, evenly spaced, and not, as they are in health, separated by a long and a short interval. It will also be observed that the heart is very irritable, easily quickened by exertion. In addition to peripheral neuritis, there is serious disease in the circulatory system, particularly in its innervation: there is dilatation of the right side of the heart, and a state of relaxed arterial tension. Paralysis of the left recurrent laryngeal nerve by a grossly distended right auricle has been recorded. There is a wide range in the pulse-pressure, and Aalsmeer and Richter have shown that there is almost invariably a low diastolic blood-pressure which can be influenced by the injection of adrenaline (the adrenaline effect). Pitressin raises the diastolic pressure from almost zero to 75 mm. and the venous pressure falls; this beneficial effect may last 1\frac{3}{4} hours.

Usually in well marked cases, the electrocardiagram shows distinct changes of low voltage and an indefinite inverted or flattened T. wave in I, II and III leads, shrinking of the P—R interval and prolongation of the Q—T interval.

The cardiac enlargement in human beriberi was ascribed by Aalsmeer and Wenckebach to cedema of the heart-muscle, which results in an interference with its contractile power without disturbance of its excitability.

Wenckebach investigated a number of cases of cardiac beriberi in the Dutch. East Indies and Singapore, taking special precautions to inject hardening fluid, and he was thereby able to confirm the presence of certain gross anatomical

changes which are demonstrable during life by radiography. The whole of the right side of the heart is enlarged, while the left remains comparatively small; the conus arteriosus takes part in the change. The large systemic veins are commonly dilated, and as much as three litres of blood may escape from the right auricle. The extrapericardial pulmonary vessels are not abnormally congested. Microscopic examination of the heart muscle after death reveals intracellular cedema, sarcolysis, and hydropic degeneration, probably primarily due to excess of lactic acid, brought about by defective oxygenation. The primary lesion is, therefore, a loss of contractibility of the heart muscle, related to water retention, with consequent loss of peripheral vascular tone. The clinical picture and its response to adrenalin and pitressin, together with the lowering of diastolic pressure, accord with these findings.

Keifer (1930) and Wenckebach (1929) excluded the previously held vagus causation of heart failure on the grounds that no evidence exists that paralysis of this nerve can produce the picture of heart failure as seen in beriberi, and that when tachycardia develops as the result of vagal inhibition by atropine the

heart decreases rather than increases in size.

Aalsmeer employed the results of these observations as a practical test to indicate the stage of the disease and response to treatment. The diastolic pressure is known as the "minimum tone pressure," because it is the pressure registered by the sphygmomanometer at the moment when the auscultatory bruit disappears with decompression of the brachial artery. The essence of the test is that, when the diastolic pressure is registered, the administration of adrenalin in hypodermic doses of 1 mgm. will be found, if observations are taken at five-minute intervals, to bring the pressure down to zero in an uncured case of beriberi. That is to say, the auscultatory murmur will persist during complete relaxation of the pressure of the artery as long as the patient is under the influence of adrenalin.

Cardiac attacks.—Most cases die from paresis and over-distension of the right heart, complicated and aggravated by cedema of the lungs, diaphragmatic paralysis, hydrothorax or hydropericardium. Sudden cardiac failure (termed by the Japanese "Shôshin") is often contributed to by the co-existence of pleural effusion, hydropericardium, paresis of the diaphragm, over-distension of the stomach by food or gas, and, above all, by cedema of the lungs. It can readily be understood how any additional obstruction of this description would still further tax the dilated, enfeebled heart and determine the fatal issue.

Subacute cardiac beriberi, as described by Casanova (1946), is really cardiac damage in patients suffering from the disease in a chronic form. Radiologically there is gross right-sided cardiac enlargement with striking pulsation in the pulmonary conus and the aorta. There is no uniformity about the cardiographic tracings in this type. Generally the P wave is accentuated. The indications are those of a sinus tachycardia with marked delay of passage of cardiac impulses through the ventricles. Administration of digitalis to this type increases the pulse rate.

Great variety in degree and combination of symptoms.—Some cases are so trifling that the patients are up and moving about with more or less freedom; others lie like logs in their beds, unable to move a limb or perhaps even a finger. Some are atrophied to skeletons, others are swollen out with dropsy, and some show just sufficient dropsy to conceal the atrophy of muscles. Though the cranial nerves above the seventh are very rarely

involved, in some the laryngeal muscles are paralysed, the patient being unable to speak above a whisper or to produce an explosive cough. one or two cases the abdominal and the perineal muscles may be so profoundly paralysed that, when cough is attempted, at most a husky expiration is produced, while the belly is bulged forward and the perineum shot downward by the sudden contraction of the muscles of expiration. The deep reflexes do not reappear for months, perhaps, after the patient is well in all other respects. In some epidemic outbreaks, as, for instance, in Iraq in 1916, an irregular pyrexia, seldom exceeding 100° F., was noted.

Uncertain course.—Beriberi slowly or rapidly declares itself after an incubation period of weeks or months; it may be preceded by a period of intermitting languor, aching legs, palpitations, breathlessness, slowly advancing cedema of legs or face; or the patient may wake up some morning and find that during the night he has become dropsical or paretic. Thus, the disease may develop slowly or rapidly. Equally uncertain are its progress and danger; within a day or a week, or at any time during its course, it may assume fulminating malignant characters. It may completely subside in a few days, or it may drag on for months. It may get well apparently and then relapse. It may, and generally does, clear up completely; or it may leave a dilated heart, or atrophied limb muscles with corresponding deformity. The variety in the severity, progress and duration of beriberi is infinite; but in all cases the essential symptoms are the same-greater or less cedema, especially over the shins; muscular feebleness and hyperæsthesia, especially of the legs; numbness, especially of the front of the shins, of the finger-tips, occasionally of the lips; liability to palpitation from cardiac dilatation, and to sudden death from the same cause.

Secondary beriberi. Beriberi manifestations produced by other diseases. Alcoholic beriberi.—It has long been recognized that alcoholic neuritis resembles in many respects the paraplegic form of beriberi. It resembles it so closely that in recent years the idea has gained ground that this resemblance is more than fortuitous, and that in both conditions there is an antecedent deficiency of vitamin B₁. The theoretical considerations advanced by Shattuck have led to the recognition of a variety of intestinal conditions in which polyneuritis may occur, such as gastric carcinoma, chronic intestinal obstruction, and ulcerative colitis, and, in the opinion of some observers, all these should be included under the heading of secondary beriberi. Cases have been reported of alcoholic addicts with congestive heart failure and polyneuritis who have recovered completely after treatment by rest, a high-calorie diet, and vitamin B₁.

Multiple factors are probably concerned in the production of alcoholic beriberi, including defects in diet and assimilation acting in conjunction with increased tissue requirements for vitamin B, due to an increased rate or type of metabolism. Many cases of alcoholic neuritis have now been cured by long-continued injections of aneurin. Weiss and Wilkins (1986) described the clinical syndrome of cardiac beriberi associated with alcoholic gastritis, which resembles the classical form of the disease. Alcohol is a significant factor in precipitating beriberi, not only because it supplies calories without B1, but also because its metabolic effect is

similar to that of pure carbohydrate. In response to aneurin the cardiovascular disorders disappear before the polyneuritis. Dysfunction of the cardiovascular system resulting from unbalanced food intake is a disease of regular occurrence in America. Tachycardia, followed by bradycardia, and gallop rhythm with electrocardiographic changes are considered to be characteristic of the beriberic heart.

Strauss thought that the polyneuritis of pregnancy may be of the same nature when pernicious vomiting occurs. In diabetic neuritis, also, it has been shown that the injection of aneurin exerts an influence upon carbohydrate metabolism.

Infantile beriberi.—This form is common in Egypt, the Philippine Islands. South China and certain Pacific Islands, and causes a high infantile death-rate. In the Philippines especially it was a terrible scourge, accounting for 10,500 deaths annually, or 28·1 per cent. of total deaths in infants under one year,



Fig. 60.—Infantile beriberi. Nauruan child in convulsions. Note general anasarca. (Dr. G. W. Bray.)

It is not necessary to regard it as resembling adult beriberi in miniature, for it differs in many essentials. The disease often occurs in the rainy season. It is never seen in Caucasians, rarely in half-castes, and should be regarded as strikingly a disease of poverty. It usually affects breast-fed infants of mothers who are either themselves victims of beriberi or subsist on a diet poor in vitamins. In Hong Kong Fehily stated that in initial, subacute and acute infantile beriberi breast-feeding immediately antedates the symptoms, but in the chronic form breast-feeding might have ceased weeks or even months previously. Removing the infant from the breast, or administering an extract of rice bran, usually leads to a rapid cure.

Haridas (1937) classifies infantile beriberi into three groups, aphonic, polyneuritic and cardiac, of which the commonest is the last, but mixed forms may occur.

The disease depends upon deficiency during uterine life and after birth of a substance in the milk which is essential to the growth and development of the child's nervous system. In the most acute type it is children previously healthy, 1½ to 3 months old, who are usually attacked; after

a series of convulsions the child suddenly dies of acute heart-failure. In less fulminating cases, vomiting, dyspnæa, dysphagia, and aphonia may precede heart-failure. The child moans or whines in characteristic fashion and the beriberic cry is diagnostic. Ptosis is also common. blood pressure is low. The total acidity and free hydrochloric acid in the gastric juice are reduced. Occasionally, chronic cases are seen in which progressive weakness and wasting, with periodical attacks of vomiting. occur. In neither form has true paralysis been noted, except that underlying aphonia which was ascribed by Kubo in Japan to a paralysis of the left recurrent laryngeal nerve from pressure by a dilated left auricle. The knee-jerks are usually absent.

In the acute type of the disease, gastro-enteric, pneumonic and meningitic signs and symptoms prevail. There is at first disinclination for food, followed by extreme restlessness, increased epigastric swelling, paroxysmal crying and general anasarca. Vomiting is the first sign of impending death. Dyspnœa and cyanosis supervene and the child dies in convulsions (Fig. 60). The temperature may be slightly raised to about 100° F.

The diagnosis of infantile beriberi is greatly aided by blood examination: a lymphopenia is almost invariably noticed, with a total absence of small lymphocytes. Bray was able to show that the therapeutic action of vitamin B. is greatly enhanced by the synergic influence of vitamin A, as in cod-liver oil.

Mortality.—The mortality in beriberi varies in different epidemics and in different localities. On the whole, it is greater in low than in high latitudes, in the dropsical than in the atrophic forms, in the acute than in the chronic. In some epidemics it is as high as 30 per cent. of those attacked; in others as low as 6 per cent., or even lower.

Wernicke's encephalopathy.—The combination of ataxia, clouding of consciousness and ophthalmoplegia was described by Wernicke in 1881 as acute superior hæmorrhagic policencephalitis. Subsequently this syndrome was associated with chronic alcoholism; from 1933 onwards its connection with vitamin B, has been suspected and a similar condition had been described in nutritional disease of silver foxes in America. The accuracy of the forecast was shown by the outbreaks which occurred in prisoner-of-war camps in the Far East. A review of 52 cases has been made by Wardener and Lennox. Other descriptions are by Spillane and Dean Smith. There were 21 deaths and the diagnosis was established at autopsy by demonstration of hæmorrhages in the mamillary bodies of the brain. In its clinical and pathological manifestations cases show no resemblance to any form of infective encephalitis. From the rapidity with which it responds to injections of aneurin this encephalopathy appears to be produced by an acute deficiency of vitamin B1. predisposing causes are dysentery, diarrhoea, failure of adaptability to a rice dietary, febrile conditions such as sepsis from gunshot wounds, and chronic malaria. The first symptom is the persisting anorexia, followed a week later by vomiting and nystagmus. Then the full picture develops of miserable inactivity, insomnia, disorientation, non-co-operation, semi-coma and severe oculomotor palsy. The eye symptoms consist of wavering of visual fields on looking to the side, diplopia, photophobia,

insomnia and giddiness. In the alcoholic type there are often residual psychotic changes and sometimes glossitis; pellagrous skin eruptions and manifestations of ariboflavinosis may coexist. In the deficiency type other forms of beriberi are associated in 90 per cent.

In the eye horizontal nystagmus is the earliest sign; in a quarter of the cases there is paralysis of the external rectus, sometimes complete disconjugate wandering, loss of visual acuity, papillædema, ptosis and retinal hæmorrhages. Other disturbances of the central nervous system consist of lesions of the trigeminal, facial, auditory and glossopharyngeal nerves.

The pathology has been discribed by Campbell and Biggart. Occasionally there are visible hæmorrhages. On section pathognomonic lesions are seen. There are foci of congestion and hæmorrhage scattered symmetrically in the grey matter of the brain stem and hypothalamic regions. The mamillary bodies are nearly always affected. The lesions show specific selectivity for the vegetative centres, being most severe in the lateral horns and Clarke's nuclei at the thoracic level. Thrombosis is rare, but there are numerous perivascular hæmorrhages with widespread degenerative changes throughout the brain. Treatment.—There appears to be unanimity that, directly the diagnosis is established, symptoms are relieved by injections of aneurin, 50–100 mgm. parenterally, daily.

Nutritional retrobulbar neuritis.—The frequency of this serious condition in prisoners of war in Japanese hands necessitates its inclusion in this chapter. It manifests itself by the loss of visual acuity with disorders of perception, such as shimmering and flickering of images. According to Dean Smith there is usually some degree of pain in 54 per cent. and the consciousness of a central blind spot is a spontaneous complaint in 6.5 per cent. Photophobia is not common and no corneal or conjunctival lesions are seen. On the other hand visual acuity is not a good guide. A visual acuity of less than 6/60 was found in a small proportion, mainly in men, but a central or paracentral scotoma was found in all and was larger for red than for black and white with constriction of visual fields. Ophthalmoscopy reveals degenerative pigmentary changes around the macula in 10 per cent. and optic atrophy in 1 per cent. Temporal pallor of the disc in 25 per cent. indicates that the condition was progressing slowly. Whitfield (1947) states that the connection with the beriberi syndrome was unequivocal. The majority had cardiac beriberi, a considerable proportion showed the orogenital syndrome and, in some, burning feet suggesting a pellagrous tendency. In a small group which were treated with multivitamin capsules—riboflavin, pyridoxin and pantothenic acid in addition to A, B, and nicotinic acid, all except one improved. Kagawa (1938) has given a comprehensive summary of Japanese literature on the association of retrobulbar neuritis with beriberi and finds it common in lactating women in the eighth to ninth month of lactation. He stresses that it is usually associated with mild chronic beriberi.

Burning Feet.—"Chachaleh" (Somaliland); "Barasheh"; "Kalerichal" (Tamil); "Gopalan syndrome"; "Dysæsthetic phenomenon" (Spillane). Pyralgia melalgia.

424 BERIBERI AND OTHER VITAMIN B₁ DEFICIENCIES

This is a very chronic condition which had been recognized in Malaya, British Guiana, West Africa and Somaliland for many years. Buchanan reported on a series of over 100 cases from Somaliland. Painful or burning feet constituted the most frequent and disturbing manifestation of malnutrition in Japanese prison camps. It is doubtful whether it should be included with the beriberi or with the pellagra syndromes. Its affinity to the latter is shown by the fact that it is mentioned by Casal and is recorded by Jansen in 1787, and was seen again in the Spanish civil war. It is doubtful whether the primary lesion resides in the nerve tissue or in the vacular supply. Before the last war it was well described by Kingsbury in Malaya. Moore, Scott, Landor and Pallister have also described neurological symptoms (weakness, ataxia, inco-ordination and loss of visual and auditory acuity) associated with burning feet in that country.

The syndrome commences with deep aching in the sole of the foot, spreading, like a toothache, to the toes and instep. The sufferings of the victims can hardly be exaggerated. Soon the whole foot is involved with the most acute "pins and needles." The pain is usually worse at night; most of the affected prisoners slept with both feet outside their blankets, but the condition progressed with excruciating bouts of shooting pains up and down the feet and calves and it sometimes took months to develop. Sometimes, too, the palms of the hands were involved. Shortly after onset delimited hyperidrosis of the affected parts appeared and was gradually replaced by ascending skin analgesia with complete insensibility to pin-pricks and cotton wool. First the ankle jerks, then the knee jerks, after some increase, slowly diminished. No loss of superficial reflexes was noted. Advanced cases showed loss of passive movements and sensation and co-ordination became rapidly inaccurate. Many developed retrobulbar neuritis and most exhibited associated ariboflavinosis phenomena, such as eczematous scrotal dermatitis, glossitis and angular stomatitis (Whitfield, 1947).

Cruickshank and Jackson (1946) recount the stirring picture of patients endlessly limping up and down between the huts throughout the night. Two types of gait were common, such as the ataxia of plantar anæsthesia, carefully picking their way like bathers walking over shingle. The physical deterioration was great. No relationship to wet beriberi was evident and response to treatment disappointing. Nicotinic acid gave temporary relief, but with an increasing supply of sova beans and rice polishings and $1\frac{1}{2}$ oz. of yeast a steady improvement occurred (Dean Smith). The work of Gopalan and Burgess (1946) seems to suggest that some other factor than the B complex is involved. Daily injections of calcium pantothenate appeared to have some effect, and it is suggested, on this basis, that the requirements of pantothenic acid depends on the carbohydrate intake. One can only surmise that it is probably a dietary insufficiency due to failure of intestinal biosynthesis.

Diagnosis.—Usually the diagnosis of beriberi is not difficult. Multiple peripheral neuritis occurring as an epidemic, or in a place or ship in which the disease has occurred on some previous occasion may, as a rule, be set down as beriberi. Sporadic cases may be difficult to diagnose, especially if there is a history of alcoholism, of malaria, or of drugging with arsenic. The presence, actual or past, of cedema—especially of cedema over the shins—and palpitations and other evidences of cardiac implication, are significant of beriberi. In the atrophic or paralytic type the jongck or "squatting test" is very useful. The patient is unable to assume, or rise from, a squatting position with his hands on top of his head. It must be borne in mind that slight anæsthesia of the prætibial skin area, slight cedema of the same region, slight hyperæsthesia of the calf muscles, and,

perhaps, impairment or absence of knee-jerk may be the only signs. Rheumatism is rare in the tropics.

Pyruvic acid determination in the blood is of diagnostic value. In acute beriberi the blood contains about 2 mgm. per cent.; in untreated chronic cases 1.5 mgm. per cent. and in those injected with aneurin about 0.5 mgm.

Meyers introduced two new tests for the diagnosis of cardiac beriberi. The first is the development of, or increase in, an audible sound in the antecubital space after subcutaneous injection of adrenalin. The second and more important is the estimation of diuresis after the fasting patient has drunk a litre of water. The volume of urine passed every half hour is charted for four hours. A normal person excretes all the fluid, but in beriberi there is water retention; this should disappear after treatment with aneurin. (Volhard's diuresis test.)

Differential Diagnosis.—Cases have been diagnosed as cardiac disease, tabes dorsalis, muscular rheumatism, progressive muscular atrophy, ascending spinal paralysis, and have over and over again been relegated to that refuge for ignorance, malaria. There should be no difficulty in distinguishing beriberi from tabes dorsalis, by the Argyll-Robertson pupil and the positive Wassermann reaction. In both paraplegic beriberi and locomotor ataxia, Abadie's sign (absence of pain on compressing the tendo Achillis) is present.

Beriberi can be differentiated from alcoholic neuritis by the tremors and mental disturbances which are generally obvious; from arsenical neuritis by the pigmentation, the diarrhea, and digestive disturbances, and by the hyperkeratosis of the palms and feet that is apt to occur in this intoxication; from chronic lead-poisoning by the blue line on the gums, the wasting of the arm and leg muscles which are most in use, the characteristic sparing of the supinator longus, and the basophilic stippling of the red blood-corpuscles; from lathurism by the presence of the knee-jerks and the absence of muscular hyperæsthesia in this affection; and from triorthocresyl phosphate poisoning (ginger or jake paralysis) which causes a flaccid form of motor paralysis. The differential diagnosis from heart disease, chronic nephritis, and ancylostomiasis is sufficiently obvious.

It may be necessary to differentiate Korsakoff's syndrome and Landry's paralysis.

Schretzenmayr described the radiographic appearances of the beriberi heart. Three stages can be distinguished; of these the second, with special enlargement of the right auricle, is regarded as characteristic of beriberi.

There are probably other forms of polyneuritis distinct from beriberi, which may closely simulate it. Possibly these infectious forms of polyneuritis are occasioned by an organism as yet undetermined. Possibly also, infective forms of polyneuritis occur in association with food-deficiency. These may account for sporadic cases in which pyrexia is prominent, and also for isolated outbreaks not apparently associated with a faulty dietary.

Famine œdema (nutritional œdema) is more pronounced than œdema of simple starvation, and other causes than mere lack of sufficient nutriment are at work. It is most pronounced in the feet and legs, and marked muscular weakness and alimentary-tract disturbance are common. It was common when there was a shortage of fats, as in Central Europe during the 1914–18 and 1939–45 wars. In Java and Haiti a form of malnutritional œdema was prevalent among individuals whose diet was inadequate, and amongst infants fed on a preponderantly starchy diet over a long period. In these a generalized dropsy, similar to famine œdema and œdematous beriberi, is observed. Famine œdema was extremely

common in Japanese prison camps in Singapore and Java during the recent war. There ensued considerable confusion with cardiac beriberi. The "hungercedem" of the Dutch was synonymous with wet beriberi of the British medical staff. There can be no doult that both existed, but that the former was most common and rapidly disappeared on an adequate dietary. This condition is probably not due to vitamin deficiency, but to lack of albumin and fats in the food. The primary effect is reduction in the plasma-protein, and is especially the case with deficiency of animal protein which results in a decrease in the plasma-albumin fraction with ever increasing globulin percentage, and ædema takes place when the plasma protein level falls below 4-5 grm. per 100 ml. (Himsworth).

Prognosis.—The tendency to dilatation of the heart is the dangerous element in beriberi; it should always dominate treatment. It is wonderful how rapidly it may come on, and how quickly it may prove fatal. Sudden deaths, occurring sometimes from syncope—from instantaneous failure, as well as from the somewhat slower process of increasing over-distension—are constantly found. An absolutely favourable prognosis, therefore, ought never to be ventured, even in the mildest-looking case, nor so long as the patient is exposed to the conditions causing the disease, or the neuritis appears to be active. That is a lesson which is often, and sometimes painfully, borne in upon the practitioner in beriberi districts.

Evidences of grave heart-implication, such as pulsating cervical vessels, equal spacing of the intervals between the sounds audible on auscultation, enlargement of cardiac dullness, especially to the right, epigastric pulsation, a rapid feeble pulse, a distended stomach, cold extremities, cyanosis, dyspnæa, and a disproportion in the strength of the heart- and wrist-beats, are significant of danger. Paralysis of the diaphraym, of the intercostal muscles, extensive serous effusions and very scanty urine are also unfavourable signs.

Vomiting.—No one can say when or how soon fatal implication of the cardiac nerves and muscle may take place, but vomiting is always an ugly and threatening symptom. The Japanese regard it as of fatal import. Marked dilatation of the stomach has a similar significance.

Prognosis is improved if the patient is placed on a non-beriberic diet and is treated with full doses of aneurin before the heart-muscle or the cardiac or respiratory nerves are gravely degenerated.

TREATMENT

The first and most important thing is the diet. From this, rice, especially white rice, should be eliminated, and some article rich in vitamins—such as beans, peas, peanuts, barley, wheaten flour (not overmilled), or oatmeal—substituted. Apart from other considerations, rice is a bad food for beriberies; it is too bulky. Eggs are valuable sources of the anti-beriberi factor, which is not destroyed, even when they are dried. Yeast has curative properties; the extract known as marmite may be given in doses of 1.5 grm. daily. Animal food, including fat and milk, must enter into the dietary for general nutritional purposes. The worst cases, particularly if there is any sign of serious cardiac implication, should remain in bed: but the mild cases had better spend the greater part of the day in the open air.

In cardiac cases, with a view to diminishing to some extent the bulk of blood in the vessels and heart, the seriously affected patients should take little fluid, and keep the bowels free by full and repeated doses of some saline aperient. Small doses of digitalis or strophanthus seem to do good. Should signs of acute cardiac distress appear, full doses—3, 4, or 5 drops of the 1 per cent. solution—of nitroglycerin are indicated, and intravenous injections of ouabaine (a French preparation of strophanthin), $\frac{1}{250}$ to $\frac{1}{60}$ gr., may be given. The dose must be repeated every quarter- or half-hour. and kept up until the threatening symptoms pass away. In suddenly developed cardiac attacks, inhalations of nitrite of amyl, pending the operation of nitroglycerin, are useful. Should signs of cardiac distension and failure persist and increase in spite of these means, there must be no hesitation in bleeding the patient, taking, if it will flow, eight or ten ounces from the arm or (this failing for any reason) from the external jugular. Often, as the blood flows, rapid amelioration of the alarming condition sets in, and the patient is, for the time being, tided over an acute danger and given another chance. The bleeding should be repeated if the alarming symptoms recur, as they are almost sure to do. Oxygen inhalations, if available, are worth trying in cardiac attacks. Pleural and pericardial effusions should be sought, and, if deemed to be interfering in the slightest degree with the circulation or respiration, drawn off with the aspirator.

The introduction of vitamin B_1 (aneurin or thiamin) as a therapeutic agent has entirely revolutionized the treatment of beriberi, and its dramatic effects are best observed in the acute cardiac cases when given in big doses. Hawes, Monteiro and Smith emphasized that it is in the acute attacks which break out without any previous warning that its effects are best seen. Wilkinson recommends immediate intravenous injection of 50 mgm. of aneurin, to be repeated two or three times in twenty-four hours until serial skiagrams show that the heart has become reduced to normal limits. In moribund patients the injection has been made direct into the jugular vein with spectacular success. There are two crystalline preparations in use for injection, Betaxan (Bayer) and Benerva (Hoffman, La Roche). These preparations normally contain 2 mgm., but the strong or "forte" dose is 10 mgm., of crystalline aneurin per ml.

By the mouth aneurin appears to be less effective. The proprietary preparation "Bemax" is widely used. Crystovibex (Parke, Davis & Co.) is aneurin in tablet form, and is issued in two strengths, 333 international units (1 mgm.) or 2,231·2 international units (6·7 mgm.). Benerva and Betaxan are also issued in tablet form for oral administration in doses of 1 mgm. each.

Hawes originally showed that active extracts of vitamin B₁, when given by the mouth, are destroyed in the stomach, but after the injection of a potent extract most striking therapeutic effects are noted. In cardiac or cedematous cases the patient, even when moribund, at first becomes restless after the injection, but no effect is noted in the pulse rate or in the diastolic or systolic pressures for an hour or more. If insufficient vitamin B₁ has been injected, there may be a return of the dyspnca, sudden collapse and death. In many cases, recovery is extremely dramatic. The dosage varies in different cases. The reaction is quantitative, and the results become apparent in the rise of systolic and diastolic blood-pressures.

In advanced paraplegic cases the results of aneurin treatment are by no means so satisfactory; whereas pain and subjective dysæsthesia are relieved, the nervous signs take a long time to disappear. In the Far East, especially in China, results are disappointing, because patients inevitably relapse when they return home and resume their polished rice dietary.

In the Far East prison camps from 1942 to 1945 Dean Smith found that great improvement took place with synthetic B complex mixture given by injections composed of aneurin 5 mgm., riboflavin 0.2 mgm., pyridoxin 5 mgm., calcium pantothenate 5 mgm., and nicotinamide 25 mgm. per 1 ml.: 2-10 mgm. of aneurin intramuscularly brought about improve-The dietary was supplemented by bran or rice ment in about ten days.

polishings (1½ oz.) and was useful in preventing relapses.

Breast-fed beriberic infants should be removed from the mother and handed over to a healthy wet-nurse, or placed on the bottle. Sometimes this is impracticable; in such cases in the Philippines a preparation of extract of rice-polishings, known as "tiqui-tiqui," has the reputation of being wonderfully efficacious. It is given to the extent of 5 ml. a day in 20-drop doses every two hours. At the end of twenty-four hours the most alarming symptoms disappear, and the child is well in three days. If the case is a very severe one, double doses should be given, and the tiqui-tiqui continued so long as there is any aphonia. Under modern conditions obviously aneurin is indicated. How found that in the most acute cases one injection of 5 mgm. aneurin, followed by 3 mgm. by mouth, sufficed. In chronic cases oral administration is satisfactory.

Excretion of aneurin.—The excretion of aneurin in the urine can be estimated, with sufficient accuracy to be of clinical value, by the thiochrome method without the use of the fluorimeter. Rapid excretion takes place in the first three hours after subcutaneous or intramuscular injection. It is suggested that a certain amount of injected aneurin is excreted before there is time for it to be stored in the tissues (Marrack and Hoellering).

Other measures.—For the atrophy of the muscles and anæsthesia of the skin, faradization and massage should be employed as soon as the muscular hyperæsthesia has begun to subside. Hot-air baths are of considerable service. Care should be taken that permanent deformity does not occur from contraction of muscles. Foot-drop should be counteracted by Phelps's talipes splint with an elastic accumulator, and any other threatened deformity appropriately met. Relapses must not be risked by a return to the original diet.

Prophylaxis.—In institutions under Government control, or in conditions in which it can be successfully enforced, there should be a stringent rule against the use of overmilled rice. To legislate against the use of white rice in countries in which rice is the staple food would not be politic, and could only lead to opposition and defeat the object in view; but the authorities, by educative methods and in other ways, can do much to eradicate gradually any prejudices there may be among the natives against undermilled rice. The committee on beriberi control of the Far Eastern Association of Tropical Medicine (1925) urged upon governments that, wherever overmilled rice forms a staple diet, steps should be taken

to discourage the use of rice from which essential food factors have been removed; that safe storage should be provided for undermilled rice; and that the use of accessory foods should be encouraged.

It is most important that a practical test should be elaborated for rice

which may cause beriberi when used as a staple article of diet.

As a prophylactic, marmite, in small \(\frac{1}{4}\)-oz. cubes, may be taken twice a week. Military and other expeditions should be warned that tinned meats are notably deficient in antineuritic vitamins and require the addition of other foodstuffs to protect against beriberi as well as scurvy. Dried eggs are especially valuable, but are too expensive to be used on any extensive scale.

Contrary to the conditions in scurvy, the human body does not appear to possess any appreciable reserve store of the antineuritic vitamin upon which to draw in a dietetic emergency. A constant supply, therefore, of the substance must always be maintained. The moral of this is, that for the prevention of beriberi for any population living on a restricted diet, such as soldiers and sailors on active service on land and sea, the germ and bran of wheat should be included in the manufacture of bread or biscuit where the rest of the ration consists of tinned or otherwise preserved foods. Diets which contain large proportions of starch and sugar should be supplemented by foods containing ample quantities of vitamin B₁. Where maize is the staple article of diet the meal should include the germ.

CHAPTER XXVII

PELLAGRA

Synonyms.—Mal de la Rosa; Mal Rosso; Alpine Scurvy; Asturian Rose.

Definition and description.—An endemic disease of slow evolution, which is undoubtedly connected with dietetic deficiencies, characterized by a complexity of nervous, alimentary and cutaneous symptoms, which make their first appearance during the spring months (sometimes the autumn), and recur year after year at the same season, remitting more or less during the winter months. It is for the most part confined to the poorer classes, especially agricultural labourers. The more distinctive features are (a) a remitting dermatitis of the exposed parts of the body; (b) marked emaciation; (c) profound depression alternating with mania; (d) a terminal confusional insanity.

It is necessary to emphasize the fact that pellagra and pellagrous states may overflow the limits previously assigned to them by older observers. The experiences of clinicians and neurologists during the recent war have led to the recognition of other syndromes related to pellagra, all of which have, in common, a nutritional basis. Therefore multiple deficiencies were frequent. Much of this knowledge is at present provisional and the reader is referred to the descriptions of retrobulbar neuritis and burning feet in the previous chapter.

Since 1912 sporadic cases of the disease have been reported in the British Isles. Many of these fall into the category of what is known as "secondary pellagra."

Geographical distribution.—Europe: Pellagra is found in Northern Portugal, in Spain, in Italy, in the south-west of France, sparingly in Denmark and in the British Isles, in the Austrian Tyrol, in Hungary, Croatia, Dalmatia, Bosnia, Jugoslavia, Bulgaria, Turkey, Greece, Corfu, Roumania. Bessarabia, Kherson, Poland and Transcaucasia. A few cases have been reported from Germany. Africa: Algeria, Tunis, Egypt, Sudan, the Red Sea coast, Rhodesia, Nyasaland, and among the Kaffirs and Zulus. It has also been recognized in Tanganyika, Kenya and on the Gold Coast. Asia: It has been reported from Asia Minor, Armenia, Syria, North Behar and Deccan in India, the Malay States, the Philippine Islands, Japan, China and Korea. An outbreak of pellagra was recorded in Nanking in 1920, in Shanghai in 1940, and by French observers in Szechuan. Yu reported typical cases in Manchuria. It was especially prevalent among Turkish troops and Armenian refugees in Palestine and Syria during the 1914-18 war. America: Canada (since 1914), the United States, Mexico, Central America, Brazil, the Argentine, Barbados, Jamaica, and probably other West India Islands. Australasia: Pellagra has been reported from New Caledonia and Australia (Melbourne).

Pellagra in Great Britain.—According to Stannus, the first authentic case in Great Britain was reported by Howden in 1866, the second by Brown in ¹ For more detailed information the reader is referred to the masterly summary by H. S. Stannus in the Tropical Discuss Bulletin, 33, 10-12, and 34, 3.

1906, and the third by Brown and Low from Shetland in 1909. In 1912 a series of six cases was investigated by Sambon and Chalmers, and in 1913 Box published his two famous cases in St. Thomas' Hospital. Since then it has come to be generally recognized that pellagra is found sporadically in lunatic asylums and other institutions, in subjects of general malnutrition. In the statistics of the Board of Control in the period 1913–1918, 45 deaths were noted. In 1922 there were 21 deaths, mostly from the Lancashire Mental Hospital, Rainhill, and during the period 1913–1928 there were 104 deaths from pellagra amongst asylum inmates.

Epidemiology and endemiology.—An important epidemiological feature of pellagra is the marked fluctuation of its prevalence from year to year. Thus, there may be long periods of quiescence, followed by years of considerable activity, during which the disease might be looked upon as a new invasion. There is no evidence that pellagra is spread by contagion. The sound may associate with the sick and remain healthy. Doctors, nurses, and attendants on pellagrins are not known to contract the disease. Pellagrous wet-nurses do not infect their charges.

Associated diseases, such as ancylostomiasis, schistosomiasis, malaria, tuberculosis, cœliac disease, idiopathic steatorrhœa, sprue, chronic bacillary dysentery and syphilis, play a very important part in favouring the development of pellagra, in accelerating its course, in modifying and aggravating its symptoms, and in determining its mode of termination.

Season.—Of all diseases with marked seasonal connection, pellagra is one of the most striking. The pellagra season varies in different localities, but is always the same in the same locality.

In Europe the disease invariably appears in manifest and epidemic form during the spring and autumn quarters, the spring outbreaks being by far the more severe, the autumnal recurrence often inconspicuous or lacking. In Egypt, according to Chalmers, there is a spring invasion in April and May, and an autumn recurrence in November. In Nyasaland, according to Stannus, pellagra seems to prevail chiefly during August, September, and October, which are the spring months in the southern hemisphere, and again, though to a lesser extent, in January, February, and March (fall recurrence). In the United States of America, owing to the vast extent of territory and great variety of climates, the periodical incidence of the disease is necessarily different in different sections. In the Northern States, as in Europe, the disease exhibits the usual well-marked double incidence, the spring outbreak occurring in May and June, the autumnal one in September and October. In the far south the disease may appear as early as January, and may be met at any period of the year. In Barbados it seems to prevail more or less from May to October or November. While the wide range of pellagra throughout the world might suggest that climate exerts no special influence, the very definite seasonal periodicity shows that climatic factors play an important, though indirect, part.

Sex.—Both sexes are liable, but in different places the disease exhibits a very different predilection for the one or other sex in accordance with the occupations and habits of the people. In the United States it is said to be more prevalent in women from 17 to 40 years of age; the debilitating effects of menstruation, pregnancy, and lactation are held to be predisposing and determining factors.

Age.—Pellagra is a disease of middle age, the majority of cases occurring between twenty and fifty. Within the endemic centres children are

attacked, and infantile pellagra is common in West and East Africa and

Southern China (see p. 439).

Occupation.—The disease prevails most of all among field-labourers. The inhabitants of towns, even of those in the very heart of intensely pellagrous districts, usually enjoy immunity. Although it has been stated that pellagra is rare in the Jewish race, it is quite common in Palestine, where it is confined to the poor town dwellers, whilst agricultural labourers for the most part escape.

The flooding of some of the Southern States in America by the overflowing of the Mississippi in 1927 afforded a practical example of the dietary factor. Pellagra, though common in these States, depends to a great extent on economic conditions. The diet of molasses and commeal contains very little of the pellagra-preventive factor, and only when the financial conditions allow can milk, eggs, etc., be purchased. The failure of the cotton crop meant poverty, reduced food, and pellagra.

Ætiology.—Pellagra was formerly ascribed to the most varied causes, such as insolation, poverty, insanitary dwellings, syphilis, irritant oils, bad weather. alcohol, garlic, onions, maize. Some regarded it as "sunstroke of the skin." "Sun disease" was an old popular name, and certainly the skin manifestations of pellagra are influenced by the action of the direct rays of the sun: This was proved experimentally, first by Gherardini, who varied the limits of the eruption by systematically displacing parts of the clothing; and later by Hameau, who obtained differently shaped patches of erythema by means of gloves fenestrated in different ways. In smallpox, and also in other exanthemata, light has a decided influence, more particularly the actinic rays, on the production of skin eruptions. Although light may influence the eruption in pellagra, this is no adequate reason for concluding that insolation is the cause of the disease, any more than that it is the cause of smallpox, and in fact other stimuli applied to the skin, such as pressure or exposure to X-rays, may cause the appearance of a pellagrous dermatitis.

Pellagra and maize.—The general opinion was that pellagra appeared soon after the introduction of maize into Europe, and that it advanced pari passu with the extension of maize cultivation and with the more general adoption of the new cereal as an article of food. For these and other reasons maize was held by many to be the causative agent of pellagra, just as a certain condition of rye was known to be the cause of ergotism; and, as in the latter case, various theories have been propounded to explain the operation of the assumed cause.

Lombroso and Bellardini, in 1871, first advanced the theory that the prevalence of pellagra in Italy was due to the consumption of diseased maize, and their ideas subsequently formed the basis for public measures against the disease in that country, as well as in Southern Europe. In Lower Egypt, as pointed out by Wilson, pellagra is common, as compared to Upper Egypt, and it is in the Delta that the proportion of land given over to maize is considerably higher than that under wheat, so the distribution of pellagra in that country corresponds to the area of maize cultivation.

Deeks in 1912, and Funk in the same year, suggested that pellagra was a disease produced by a deficiency in diet. In 1914 Goldberger and Wheeler fed a squad of eleven prisoners on a rich carbohydrate diet deficient in proteins. After five months, six developed cutaneous symptoms suggestive of pellagra (the first lesions consisted of an erythematous patch on the scrotum). An experiment in the converse direction also proved successful, for, by substituting a rich protein diet for one consisting in great part of carbohydrates, they succeeded in

banishing pellagra from an orphanage asylum in which up to that time pellagra had been in evidence. In 1917 Goldberger successfully disposed of the "infection theory" by obtaining sixteen volunteers who attempted to infect themselves by ingesting skin scales and naso-pharyngeal secretions of pellagrins over a period of six months. They remained quite healthy. In 1919 the commission which investigated the prevalence of pellagra amongst the Turkish prisoners in Egypt attributed the cause to a primary deficiency of "biological proteins" (B.P.V.=Biological protein value).

Although epidemics of pellagra are found usually amongst maize-eaters, many isolated cases arise under a variety of circumstances. It appears that the true cause of pellagra is much more complicated and consists in the disturbance of a delicate chemical balance between certain toxins, present in relatively large amounts in maize, and some essential dietary factors. Nicotinic acid and tryptophane are two of the latter, but the chemical composition of the poison, or poisons, is unknown. Analogues of nicotinic acid can produce pellagra-like effects in animals, but it is uncertain whether these are the poisonous substances present in maize. The problem of pellagra is therefore an intricate problem of biochemical balances.

The Vitamin B₂ Complex.—Goldberger, who at first believed that an amino-acid deficiency was the cause of pellagra, in 1922 obtained evidence pointing in another direction. Having discovered that yeast was effective in preventing and curing blacktongue in dogs, generally considered to be analogous to pellagra, Goldberger and Tanner tried the effect of yeast as a prophylactic in the human disease, and found that 30 grm. daily of brewers' yeast gave complete protection. This would supply less than 15 grm. protein, and later it was found that an acid preparation of yeast, which contained very little protein-nitrogen, in doses of 15 grm. daily, was equally effective. A PP (pellagra-preventive) factor was therefore postulated in yeast and other foodstuffs. As the result of these investigations on man and experimental work on rats, Goldberger and his colleagues were able to identify the PP factor with a vitamin in the yeast-vitamin complex differing from aneurin in its stability to heat and its distribution in foodstuffs.

It was subsequently discovered that the PP factor was in fact composed of elements of the vitamin B complex, the chief constituent of which was nicotinic acid or nicotinamide. Modern opinion is that riboflavin (the typical vitamin B₂) is concerned in the genesis of several of the more prominent pellagrous lesions. "Ariboflavinosis" is quite distinctive and has been well described by Sydenstricker.

Liver and meat contain a high proportion of nicotinic acid and this explains the well-ascertained fact that these substances are effective in the treatment of pellagra in man, as well as of blacktongue in dogs. Nicotinic acid and riboflavin have been found to be efficacious in the treatment of pellagra (see p. 441).

Although there can be no doubt that deficiency of nicotinic acid causes pellagra, the relation of the disease to the amount of this vitamin in food and the association of pellagra with maize is not yet quite clear. Maize contains less nicotinic acid (1–1.6 mgm. per 100 grm.) than wheat (4 mgm.), but more than rye, millet and refined flour. It is possible that the nicotinic acid in maize is, in some ways, unavailable.

The not infrequent occurrence of secondary pellagra is probably due to non-absorption of the necessary vitamins by a diseased or non-functioning mucosa.

Pathology.—The pathological features essential to pellagra may be obscured by complicating diseases, such as bacillary dysentery and tuberculosis. The morbid anatomy is neither constant nor characteristic; for this the chronicity of the disease, the variety of the symptoms, and the many intercurrent affections

which may arise are responsible.

A constant and striking feature is the great emaciation. The viscera show chronic degenerative changes, particularly fatty degeneration, and a characteristic deep pigmentation. The intestinal walls are greatly attenuated through wasting of their muscular coat, while at the same time the mucous lining is hyperæmio and, not infrequently, ulcerated. The liver and spleen are usually atrophied. The suprarenal capsules may be atrophied and the cortex may be black, while the medulla is whitish and may be the seat of hæmorrhages. The heart is usually in a condition of brown atrophy and weighs only 2–3 ounces.

There may be milkiness, thickening of the meninges and sometimes odema of the brain. In the cord the lateral columns and the crossed pyramidal tract are especially implicated, but the direct cerebellar tracts usually escape. The anterior cornual cells are frequently atrophied and deeply pigmented. The posterior columns do not escape, the median portion often being degenerated. The degenerative changes in the lateral columns are chiefly in the middle and lower thirds of the dorsal region, those of the posterior columns principally in the cervical and upper dorsal region. The cerebro-spinal fluid shows little change;

there is usually no increase in the globulins.

Mott remarked on the changes in the cerebrum, cerebellum, pons, medulla. and spinal cord that in none of the sections is there any evidence of meningeal or perivascular infiltration with lymphocytes, plasma cells, or polymorphonuclear leucocytes. All the changes were like those produced by a chronic toxemia, possibly in the manner already suggested. The posterior spinal ganglia cells show, in varying degree, a pronounced chromatolysis, swelling of cells, and disappearance of Nissl's granules, and all the anterior-horn cells and their homologues in the medulla and pons a varying degree of perinuclear chromatolysis. With the Marchi method, degeneration is most definite in the column of Goll. most cases the afferent tracts are more affected than the efferent. There is usually marked chromatolysis of the cells of Clarke's columns. The Betz cells of the cortex and the cells of Purkinje showed similar changes, but in a lesser degree. There is also atrophy of pyramidal cells in that part of the layer which lies on the ventricular surface of the fascia dentata. In short, the changes in the central nervous system resemble those of central neuritis (Adolf Meyer) or of subscute combined degeneration of the cord. Greenfield and Holmes thought that the pellagrous changes differed from those of the latter in the absence of gross distension of the myelin sheaths.

Shattuck drew attention to the close ætiological relationship between beriberi, Korsakoff's syndrome, pellagra, central neuritis, and subacute combined degen-

eration of the cord.

Central neuritis, which is undoubtedly allied to pellagra, was first described by H.H. Scott on sugar estates in Jamaica, and it was subsequently found in Sierra Leone and Nigeria. The central nervous lesions are widespread; the peripheral nerves are demyelinated and the posterior root ganglia of the spinal cord show degenerative changes. The medulla, cerebellum, basal ganglia and optic nerves are also affected.

Clinical pathology.—There is hypochlorhydria in 40 per cent., and quite frequently achlorhydria. In advanced pellagra there is usually anæmia, which is of macrocytic and hyperchromic type in about 50 per cent.: microcytic in the other half. The total leucocyte count is not disturbed, though there is often lymphocytosis. An indirect van den Bergh reaction is usually present in the serum. There is no change in the corpuscular fragility; the plasma albumin is diminished.



PELLAGRA RASH ON FEET

Dorsa of feet had been exposed to sun in area between turned-up trousers and uppers of shoes,

PLATE VIII

The fæces are pale, foul, milky, soapy, sometimes steatorrhœic. The urine is generally alkaline and may rapidly become ammoniacal. It may also contain tube-casts, traces of albumin and, usually, indican. Much attention has recently been drawn to the excretion of coproporphyrin (porphyrinuria) and speculations have been made regarding its significance. Some regard it as indicating faulty liver metabolism; others as the result of abnormal intestinal absorption. As stated by Beckh and Ellinger, it is specially found in secondary alcoholic pellagra, but Spies, Cooper and Blankenhorn showed that the amount of coproporphyrin in the urine appears to be proportional to the nicotinic acid intake.

Symptoms.—The cardinal signs of pellagra constitute the well-known diagnostic triad: "diarrhœa, dermatitis and dementia." The course is generally long and irregular, one of repeated exacerbations and periods of quiescence. The initial symptoms are composed of mingled psychical and digestive disturbances which may recur for years without the appearance of skin eruptions. The patient is pale, has a peculiar lifeless staring look, with dilated pupils, and complains of headache, giddiness, and vague but often severe pains in the back and joints. The scleræ are bluish and leaden coloured. The eyelids move sluggishly; the complexion is muddy. The character changes, becoming irritable, and at the same time stupid and morose.

Observations on children in pellagrous families in the United States show that many have clinical signs of pellagra. They are below the normal weight and height for their years; they make slow progress at school, show lack of interest, inability to concentrate and have poor appetites. Their

hearts are irritable and they may have tachycardia.

The earliest signs of a pellagrous tendency are difficult to define, as there are probably a great many people who suffer from chronic ill-health and are really in the pre-pellagrous state. This tendency may manifest itself by a peculiar stomatitis with erosions at the angles of the mouth (angular stomatitis) (Plate IX). There may also be an atrophic condition of the lips (perlêche) or cheilosis (see p. 438). The pellagrous process may not proceed beyond this stage. On the other hand, it may be progressive and advance to a fully developed syndrome. Then the gums may be swollen and bleed easily, a condition which gave rise to the term "Alpine scurvy." There may be eructations of gas, nausea, and vomiting. The appetite is variable. The epigastric region and, sometimes, the lower abdomen are tense and painful. Constipation may be present, but in rare instances there is diarrhee of pale fermenting stools resembling those of sprue.

The pellagrous rash.—Most observers regard the skin lesions of pellagra as early manifestations, but they are symptomatic of the underlying constitutional disturbances. At first an erythema, not unlike a severe sunburn, is observable on the parts of the body which are, as a rule, unclothed and exposed to the sun (Plates VIII, IX). The eruption is symmetrical and characteristic. It appears suddenly, first on the back of the hands and feet, then on the forearms, legs, chest, neck, face, and, it may be, on the scrotum or on the female genitalia, anus and other regions subject to mechanical irritation. Patches of erythema are irregular in outline and intensity. Very characteristic is a symmetrical eruption behind the mastoid processes,

a ring or collar round the neck (Casal's necklace), and a butterfly patch over the bridge of the nose resembling lupus erythematosus. The affected area is swollen and tense, and the seat of burning or itching sensations which become particularly acute on exposure to the sun. The congestion disappears completely, but temporarily, on pressure. Petechiæ are common on the affected parts; blebs with clear, opaque, or blood-stained contents of feebly alkaline reaction may form. The eruption usually lasts about a fortnight, and is followed by hyperkeratosis and desquamation, which leaves the skin rough, thickened, and permanently stained a light seria. This is especially marked on the back of the hands and on the elbows, thus constituting recognizable evidence of pellagra. Hyperkeratosis may occur on the soles of the feet and as diffuse thickening over the knuckles. In severe cases the skin over a large area of the body comes to resemble that of a roasted turkey. Ichthyotic changes sometimes supervene and may be more intense in winter than in summer. It is on account of this roughness of the skin that the disease was originally called "pellagra" (an Italian word derived from pelle (skin) and agra (rough)).

"Purpura provocata" may precede or follow erythema. This has a linear distribution. Hæmorrhagic stripes of considerable length have been seen, especially after exposure to the sun and after trauma. This phenomenon is an indication of the permeability of the blood vessels (Simons, 1946) and was observed in prisoners of war in Java.

Stannus has suggested, as a result of the work of Lewis on the bloodvessels of the human skin and their responses, that the skin lesions in pellagra are due to the liberation of histamine and its action upon the blood-vessels, and that the mechanism underlying the affections of the

mucous membranes is of a similar nature.

Exposure to light appears to be the precipitating factor. Ruffin and Smith showed that radiation may evoke not only skin lesions, but also associated oral, gastro-intestinal and neurological manifestations. Since injections of porphyrin can sensitize normal persons to sunlight, it has been suggested that there may be abnormal porphyrin metabolism in pellagra.

The burning sensation in the soles of the feet and palms of the hands which is such a common symptom in pellagra may be ascribed to the same cause. Naturally, the appearances of pellagra differ considerably in different

races. What is an erythema in the European becomes a blackish or purplish patch on the skin of a negro. In olive-skinned races pellagrous patches assume a sepia colour.

The pellagrous rash has to be differentiated from follicular hyperkeratosis or keratosis pilaris, which is common in ill-nourished natives in all warm climates. Dry, hard or, it may be, pigmented, papules are formed which project from the hair follicles as spiny processes. The surrounding skin

is dry and rough.

Implication of the nervous system is indicated by tremor of the tongue, exaggerated deep reflexes, and mid-dorsal spinal tenderness. tremors of the extremities, especially of the head and the hands, are frequently noted and become more marked as the disease progresses. Muscular cramps may occur; definite ankle clonus, spasticity and extensorplantar response are often seen. The patient suffers from obstinate





Fig. 1.—Characteristic inflamed tongue of acute pellagra with angular stomatitis.

Fig. 2.—Early pellagrous rash, with cellular infiltration and pigmentation.

Fig. 3.—Typical pellagrous rash over occiput and mastoid processes, with formation of "rosary" round neck.

J. I. Enright:







Fig. I.—AMŒBIC DYSÈNTERY. Typical patches of infiltration and ulceration of ascending colon, showing "Dyak-hair" sloughs. Fig. 2.—BACILLARY DYSENTERY (Sonne infection): Acute Sonne dysentery in a child, showing bright pink hyperæmia of muscular coat. Fig. 3.—BACILLARY DYSENTERY (Shiga infection): Coagulation necrosis of lower portion of ileum, showing characteristic green coloration of the destroyed mucous membrane.

sleeplessness, occasionally from uncontrollable sleepiness. He experiences great weakness, especially in the lower extremities, and is subject to peculiar attacks of giddiness, with a tendency to fall forwards or backwards. Chvostek's sign-mechanical irritability of the facial nerves-is present in the majority of cases. A very characteristic symptom is pyrosis, or a burning sensation down the cesophagus (dysphagia). This frequently creates the idea in the patient's mind that his food does not agree with him, or even that attempts are being made to poison him. The pupils are dilated and there is usually photophobia. The arms may be spastic and movements are accompanied by a coarse tremor, which is increased on exertion.

Sydenstricker (1941), in a large series of pellagrins, found that spinal cord changes were present in 6 per cent. and polyneuritis in 2.8 per cent. Spillane observed neurological signs and symptoms in individuals who had passed through several relapses. Out of 30 there were pyramidal signs in 16, absent deep reflexes in 3, reduced superficial sensation and loss of vibration sense in others.

In the early stages the manifestations are mainly psychoneurotic, but later polyneuritis may appear. General deterioration of mental and physical health may antedate the continued manifestations of the disease. Acute mania and confusion may herald the end. Thus pellagra may not only produce insanity, but it may result from it.

After the disappearance of the eruption, atrophic patches of skin remain in the interdigital clefts, and these, together with muscular wasting, give the appearance of washerwomen's fingers. The hands, in fact, are aged out of proportion to the rest of the body. The nails become atrophied and brittle.

As a rule, there is no marked permanent elevation of temperature, but

periods of slight fever occur at irregular intervals.

Ocular changes in pellagra.—The bulbar conjunctiva is ædematous showing linear erosions on the temporal side of the palpebral aperture. Corneal dystrophy is frequent. Small ovoid opacities lie deep in the corneal stroma. Lens opacities are of three types: powder-like opacities, multiple irregular opacities, and tongue-like opacities extending from the peripheral zone towards the centre of the lens. All these are associated with acute avitaminosis B2.

Progress.—Two or three months after onset the symptoms abate and, although the affected skin areas remain dark and rough, the disease appears to be arrested. Next spring, however, the whole series of phenomena recurs in a more severe form. The eruption assumes a darker colour. The depression of spirits deepens into melancholia, which may have maniacal interludes, with a peculiar tendency to suicide, especially by drowning. The general feeling of weakness increases; the patient loses weight and is unable to work; his gait becomes uncertain and somewhat of the spastic paraplegic type. The tongue is tremulous. The pains in the head and back become very acute, and there may be lightning pains, cramps, twitchings, tremors, and even epileptiform seizures of the cortical type. Diarrhoea may now be troublesome.

For several years the disease may thus recur in the spring with increasing severity. The patient becomes greatly emaciated, paralytic, and completely demented. Helpless, bedridden, suffering from incontinence of urine and uncontrollable diarrhea, covered with bedsores, and neglected, he dies from exhaustion or from some intercurrent disease.

The duration of pellagra is exceedingly variable. It may last only two or three years: it usually extends to ten, fifteen, or more.

Cases differ considerably. The obscure forms are probably much more common than the fully declared disease. They were formerly known—somewhat incongruously—as pellagra sine pellagra.

Ariboflavinosis.—The riboflavin deficiency syndrome is now regarded as typical of "pellagra sine pellagra." The following signs are character-



Fig. 61.—Avitaminosis B, in a West African negro. Characteristic facies of ariboflavinosis. (Dr. D. Fitzgerald Moore.)

istic of it: angular stomatitis1 and facial lesions consisting of filiform seborrhæic excrescences (dyssebacia), varying in length up to 1 mm., sparsely scattered over the face. The mouths of the sebaceous glands are plugged with inspissated sebum, giving the skin a roughened appearance, which on the shoulder, arms and legs is known as phrynoderma or toad's skin. The evelids show dermatitis lesions, may be macerated and stuck together. Fissures and maceration at the angles of the mouth are seen, and a degenerative crust-like formation on the epithelium of the lips, most marked on the lower. The lips, particularly the lower, frequently show a marked increase in the vertical fissuring (perlêche) (Fig. 61). A specific glossitis has been described: the tongue is clean, the

papillæ flattened or mushroom-shaped and the colour definitely purplish red or magenta, in contrast to the scarlet tongue of nicotinic acid deficiency. (Plate XVII.)

The ocular manifestations are burning, lacrymation, photophobia, blurred vision, inability to see in a dim light and visual fatigue. The earliest and most common sign is circumcorneal injection and, when viewed by a slit lamp, there is marked congestion and proliferation of the limbic plexus, with the production of great numbers of narrow capillary loops. The lesion progresses to vascularization of the cornea within a week, if treatment with riboflavin is not given. Eventually keratitis is produced, similar to that associated with acne rosacea, which is also amenable to riboflavin therapy. It is probable that ariboflavinosis is also responsible for retrobulbar neuritis, which may also be part of the pellagra syndrome (see p. 423).

¹ The term "cheilosis," or "cheilitis" applied by some writers to lesions at the angles of the mouth, should be reserved for lesions on the lips.

Other less marked varieties (Formes frustes).—Corkhill and others have pointed out that there are quite a number of subclinical cases in which physical signs are less obvious, but symptoms appear only after undue fatigue.

In some the nervous symptoms predominate, in others the gastro-intestinal; in others again the cutaneous. Forms of hyperæsthesia may occur in different regions of the body, especially the feet (p. 423). Ocular symptoms, such as ptosis, diplopia, retrobulbar neuritis, amblyopia, mydriasis, are not uncommon. The Plummer-Vinson syndrome of glossitis and dysphagia, with angular stomatitis, koilonychia and anæmia, in aged women, is possibly a pellagrous manifestation.

Infantile pellagra.—Pellagra in childhood is very apt to be overlooked. especially in native races. The children become irritable, their skin and hair tend to lose the normal colour and glossiness, and there may be attacks of diarrhœa with transient cedema of the hands, feet, and face. After ten days or so pigmented patches appear on the skin of the extensor surfaces about the ankes, knees, wrists and elbows, and these blackened patches appear first where there is any focus of irritation or pressure. Trowell described infantile pellagra in E. Africa as a syndrome of which the principal signs are cedema, dermatitis and diarrhœa. Infantile pellagra has also been reported in American negroes, from Mexico, Cuba. Costa Rica and S. China. It has to be distinguished from malignant malnutrition (p. 446).

Pellagra typhus.—In this very acute type there are intense prostration, high temperature, muttering delirium, pronounced nervous tremor, generalized rigidity, and convulsions. In extensive outbreaks of pellagra, such as occurred among the Turks during the 1914–1918 war, cases of this description were comparatively common.

Terminal stages, pellagrous insanity.—Mental symptoms supervene in one-third to one-quarter of all cases.

It has been estimated that from 4 to 10 per cent, become permanently insane. In the United States of America pellagrins have become numerous in the lunatic asylums. The type of insanity is usually a most profound melancholia with a suicidal tendency; cases may resemble in their clinical features general paralysis of the insane. Epileptiform convulsions may occur.

The time of the appearance of mental symptoms is subject to the widest variation. They may be primary symptoms, or occur during convalescence. The mental aberrations may be characterized by profound dementia, hallucinations, and katatonia. As a rule, restlessness, vertigo and insomnia anticipate the characteristic melancholia. In general, the patients exhibit anxiety neurosis with depressive features. Pyschosensory disturbances are common, with intolerance of bright light, colours and noises. The patients are fidgety, quarrelsome and irritable. In spite of increased motor drive, they complain of weakness and fatigue.

Not only may pellagra lead to insanity, but those insane from other causes are very liable to pellagrous manifestations. Goldberger found that in certain asylums in the United States the number of lunatics developing pellagra each year was a constant proportion of the total. In England,

pellagra has been noted in lunatic asylums since 1913. Watson, in a review of the pellagra cases in the Rainhill Asylum, Lancashire, found that at the time of onset they had been resident from six months to several years.

Pellagrous encephalopathy has to be differentiated from Wernicke's encephalopathy. In the latter there is nystagmus and ocular palsies. A process of acute cerebral disturbances responding to nicotinic acid has been described in alcoholics, the aged poor, in persons depleted by illness or operation and in certain therapeutic procedures (hydration). Patients with stupor, delirium and variable reflex changes respond remarkably to the administration of nicotinic acid (Graves, 1947).

Secondary pellagra.—Pellagra due to voluntary restrictions of diet has been recognized by several observers during recent years. Mook and Weiss described the typical clinical picture of pellagra in a young woman on a slimming diet; Mumford, Carley and others found it in mature women who, for some faddist cult, had been subsisting on an unbalanced dietary; Guthrie, Green, Walker and Wheeler reported similar phenomena in patients on a ketogenic régime. It is stated that hyperthyroidism pre-

disposes to pellagra.

Pellagra in all its varied manifestations may be associated with some organic lesion in the gastro-intestinal tract, such as œsophageal stricture. carcinoma of the stomach, pyloric ulcer, pyloric stenosis, carcinoma of the ileum, stricture of the rectum, rectal polyposis, suppurating hydatid cyst. Crohn's disease, chronic amœbic dysentery, cœliac disease, idiopathic steatorrhœa, or even tropical sprue. When the avitaminosis follows surgical operations, such as partial colectomy, on the gastro-intestinal tract or elsewhere, it is known as surgical pellagra. Alcoholic pellagra is applied by American observers to the disease in chronic alcoholics, especially those who drink methyl alcohol. It has been suggested by Stannus, by way of explanation, that gastritis is the one common factor which supports the hypothesis that, primarily, in pellagra the fault may lie in the intrinsic factor of the gastric juice. On the other hand failure of biosynthesis of vitamins affords an explanation for the sporadic occurrence in sufferers from chronic gastro-intestinal disease. In this respect it has been found that sulphonamides are capable of interfering with the action of certain intracellular enzyme systems in which components of the vitamin B complex take part.

A case of acute pellagra with toxic confusional psychosis and skin manifestations in a man suffering from tuberculous peritonitis, following upon isoniazid (isonicotinic acid hydrazide), has been described by McConnell and Cheatham (1952). The dose was 3-5 to 5 mgm. per kg. for three months.

Diagnosis.—Doubtful cases are occasionally encountered, but localized erythema associated with nervous, particularly mental, symptoms, great debility, and seasonal recurrence, in a person in or coming from a pellagrous district, can hardly be confounded with any other disease. The rash may be mistaken for acrodynia, erythema multiforme, dermatitis venenata, eczema solare, trade dermatitis, lupus erythematosus, syphilis, or poison-ivy dermatitis. "Crazy pavement" skin lesions, which are

common on the legs of ill-conditioned natives, are not necessarily pellagrous, but are more distinctive of kwashiorkor. The gastro-intestinal disturbance and glossitis have to be distinguished from sprue; while the nervous manifestations have to be differentiated from hysteria, cerebral syphilis, general paralysis of the insane, ergotism, and lathyrism. In old people with arterio-sclerotic changes and accompanying mental symptoms, there may be lesions of hands and feet which may be a source of confusion. "Pink disease" in children may also be mistaken for pellagra, as the distribution of the skin lesions is very similar.

Treatment.—After the end of the 1914–1918 war and the formulation of the biological protein theory, many workers, notably Goldberger and Wheeler, noted that improvement in the pellagrous lesions, and even in the nervous involvement, followed a liberal dietary rich in proteins and in vitamins. Then ensued a period in which liver and yeast extracts, notably marmite, were given an extensive trial, but it was generally conceded that, though the therapeutic secret was locked up in the vitamin-B complex, vitamin B_1 was not the main factor.

In 1937 Elvehjem, Madden, Strong, and Wooley reported the cure of blacktongue in dogs by the administration of nicotinamide prepared from yeast. Shortly afterwards Spies, Cooper, and Blankenhorn recorded the successful treatment of human pellagra cases. These patients were in hospital and received a controlled basal diet, upon which alone symptoms had shown no improvement. Relatively large doses of nicotinic acid were given—40-80 mgm. by injection, or 200-1,500 mgm. by the mouth within a period of twenty-four hours. Almost simultaneously, Fouts, Helmer, Lepkovsky, and Jukes reported the cure of four cases of "alcoholic pellagra" treated on the same lines, there being improvement in the mental condition, stomatitis, and the intestinal disorders, as well as cure of the dermatitis. Spies, Bean, and Stone (1938) then published a series of 73 cases of endemic pellagra and 99 of "subclinical pellagra", and stated that they had not observed a single acute case that had not responded promptly to nicotinic-acid therapy. Also, in a special study by Spies, Aring, Gelperin, and Stone of 60 cases showing acute mental disorder, improvement was observed within periods of ten hours to six days after nicotinic acid medication, the daily dosage being 500-1,000 mgm. by mouth, or 100 mgm. intravenously. Further confirmation soon came from Matthews, who studied 13 cases of classical endemic pellagra maintained on a pellagra dietary. These favourable results in American pellagra have received a considerable degree of confirmation in the hands of Alport, Ghaligoungui, and Hanna in Egypt, and also of Ellinger, Hassan, and Taha (1937). They treated 15 cases with nicotinamide (Merck), the dose being 1 grm. daily by the mouth or 0.5 grm. by subcutaneous injection. On the whole, they found that acute inflammation of the tongue and ulceration of the mouth subsided in five to seven days, and the sense of taste returned in the same time; in one case colic supervened almost immediately, suggesting intolerance. Thus nicotinamide effected great improvement in the acute mucous membrane lesions, as well as in the skin condition; on the other hand, chronic skin lesions, friction areas and chronic changes in the tongue were only slightly affected. The appetite, mental condition and general physical health were all improved. Grant and Spies recorded that ptyalism, Vincent's infection and coproporphyrinuria disappeared, and Hawksley found great change in the follicular hyperkeratosis on and around the naso-labial folds.

Polyneuritis and other neurological phenomena do not respond to nicotinic acid and therefore aneurin has been recommended, but it appears to result in increased excretion of riboflavin. There are good reasons for assuming that in pellagra there are multiple deficiencies. A high calorie diet of 3,000–4,000

calories, with ample supplies of fresh meat, liver, milk and eggs, supplemented by some of the vitamin B complex, such as yeast 1-2 oz. daily, is recommended.

Since the discovery of ariboflavinosis as part of the pellagra syndrome most authorities reinforce treatment with riboflavin tablets in doses of 1–3 mgm. daily. During the recent outbreak of pellagra in Hong Kong Wilkinson found the effects of intravenous nicotinamide injections almost dramatic. Patients who were disorientated, rambling in speech and unable to co-operate or swallow, became hungry and rational within 72 hours. (In acute pellagra the blood nicotinic acid was found to be 0·31 mgm. per cent. and to rise on treatment to 0·55 mgm. per cent.) In cases with rapidly increasing reduction of visual acuity, associated with concentric constriction of fields of vision, response to nicotinic acid and riboflavin daily changed the vision from 6/60 to 6/9 or 6/6 within a week.

The evidence that nicotinic acid is a specific cure for pellagra and for the somewhat similar nutritional diseases produced by maize diets in dogs and pigs (Chiek, Macrae, and Martin) thus appears to be conclusive, and it is now reasonable to ascribe the curative value of liver extracts and yeast, formerly observed in pellagra, to their nicotinic acid content. Ruffin and Smith (1937) found that, whereas crude liver products were effective in relatively small doses in canine blacktongue and in pellagra, larger amounts of more purified extracts were ineffective. These observations, which suggest that a combination of two substances is needed to correct deficiencies in diets which induce blacktongue and pellagra, are difficult to reconcile with the curative effect of such simple substances as nicotinic acid and nicotinamide.

The reaction to nicotinic acid in normal individuals is tingling and increased warmth over the malar regions and neck. Sometimes nausea, vomiting, abdominal cramps and urticaria may ensue. Nicotinic acid and nicotinamide are now dispensed in a convenient form in tablets of 30 to 50 mgm. each. In mild cases 50 mgm. is given three times daily (150 mgm.) for ten to fourteen days, and double that quantity (800 mgm.) in more severe cases. The effect upon the pellagrous rash is impressive. Sodium nicotinate (nicotinamide) has the same action, but without any unpleasant side effects. Overdosage with nicotinic acid causes some tingling and numbness of the tongue, and also in the lower jaw along the course of the inferior dental nerve. Riboflavin in maximal doses (3 mgm.) should be added in cases exhibiting signs of ariboflavinosis. The most striking and most easily observable effect of this mode of treatment is seen in the amelioration of the tongue and mouth symptoms. It has a profound effect upon the psychology of the patient as well as on the processes of digestion and assimilation.

Treatment of infantile pellagra.—Gillman (1946) has proved that gastric extract (ventriculin) is the most satisfactory form of treatment. He further states that the addition of vitamin concentrates and iron significantly diminishes its effectiveness.

Treatment of mental symptoms.—Spies, Aring, Gelperin and Bean submitted 60 cases with mental manifestations to treatment with nicotinic acid, in maximum doses, and coramine (the diethylamide of nicotinic acid). These cases showed loss of memory, delirium, mania, or depression; some

had a paranoid reaction. Recovery took place in all within six days. Korsakoff's psychosis and manic depressions were not influenced in the same way. Coramine is injected in doses of 2–5 ml. daily or by the mouth, to a total of 20–50 ml. Those cases with spinal symptoms are singularly resistant to treatment.

Treatment with allied preparations.—Certain of the pyridine carboxylic acids exhibit anti-pellagrous properties. Bills, McDonald and Spies found that pyrazine 2–3 dicarboxylic and pyrazine monocarboxylic acid act like nicotinic acid, curing glossitis and dermatitis. Vilter and Spies claimed that quinolinic acid (2-3-dicarboxylic acid of pyridine) has a therapeutic action on the tongue and mouth symptoms.

Prophylaxis.—In view of the volume and importance of recent researches in this field, it is evident that the prophylaxis of pellagra is bound up in public-health measures and especially in ensuring a well-balanced protein dietary. Whether pellagra can be prevented by the prophylactic administration of nicotinic acid and riboflavin remains to be seen.

CHAPTER XXVIII

SCURVY IN THE TROPICS

Epidemics of scurvy are apt to occur among gangs of coolies and labourers who are fed on an unsuitable dietary, especially in natives recruited for labour purposes and fed upon dried cereals and preserved foods, who previously had been in the habit, in their own villages, of subsisting on large quantities of fresh vegetables and fruit such as bananas.

Ætiology.—Scurvy is a food-deficiency disease. It is produced, not by general starvation, but by the absence of an accessory food factor, or vitamin, which can now be prepared synthetically and is known as ascorbic acid. This body is present in all fresh vegetables, including swedes, turnips, and onions, and in fresh fruit, especially the orange and lemon. It is very sensitive to prolonged heat and drying, and therefore is absent from tinned fruits and vegetables, and from dried legumes such as peas and beans, but re-appears directly the latter are induced to germinate. Yeast, fresh meat, and milk contain only small quantities of the antiscorbutic vitamin, and, curious to relate, according to Chick and Hume, preserved lime juice little or none at all, while preserved lemon-juice is rich in this substance.

Symptoms.—The onset of scurvy is insidious, with loss of weight, progressive weakness and pallor, and a feeling of stiffness in the leg muscles. The gums soon become affected with a swelling and sponginess of the alveolar margin. As the disease progresses, fungating masses project beyond the teeth, which loosen and fall out. The tongue swells, the salivary and lymphatic glands enlarge, and the breath becomes very foul. The skin becomes dry and rough, and very soon subcutaneous petechiæ form on the limbs and trunk, commencing around the hair follicles, especially on the thigh (Fig. 62). Hæmorrhages occur into the muscles of the thigh and into the knee-joint. Very painful

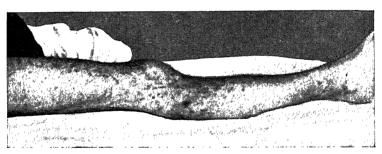


Fig. 62. Scurvy rash in sprue, showing distribution of petechiæ round hair follicles.

effusions under the periosteum form irregular nodes, which may break down and ulcerate. Œdema of the ankles is common, and hæmoptysis or hæmatemesis may occur. Any injury is apt to cause a hæmorrhage.

Together with these objective symptoms the patient experiences cardiac distress, with irregularity of the pulse and hæmic bruits at the apex. The urine is generally loaded with albumin. On the other hand, the digestive system is not disturbed, constipation being more common than diarrheea. The psychical

disturbances are pronounced. Headache is noted early, and delirium supervenes in the later stages. In the most advanced cases the jaw-bones generally become necrotic.

In the young the formation of a "scurvy rosary" at the junction of the costal cartilages, and separation of the epiphyses of the long bones, may occur in a variety known as infantile scurvy, or Barlow's disease.

Scurvy was formerly noted as endemic in the mine-workers on the Rand. Darling and others observed that a certain proportion of these cases was distinct in a clinical sense from those seen elsewhere. In this variety, known as Rand scurvy, the spongy gums and loose teeth that occur in the classical type of the disease were absent, while the heart underwent primary hypertrophy, with subsequent dilatation, suggestive of beriberi, though the neuritic symptoms of beriberi were absent, and the knee-jerks exaggerated. Rand scurvy occurred especially among gangs of native labourers when fed upon an unsuitable dietary, particularly natives from the Congo and tropical Africa, who were in the habit of consuming large quantities of fresh vegetables and fruits, and who, when in the mines, were fed on dried cereals and preserved foods. The number of these cases was very large indeed. Donaldson reported that in 1920 more than 200 cases of scurvy were treated in one hospital, of which one-third occurred within three months of entering the mines. It was found that scurvy in these natives predisposed to all kinds of bacterial infections, and especially to pneumonia. Where the diet was deficient, but not entirely lacking in vitamin C, actual symptoms of scurvy did not manifest themselves, but such individuals were very liable to bacterial infections owing to degenerative changes in the bone-marrow.

Diagnosis.—To diagnose scurvy under modern conditions is no difficult matter; but care must be taken to distinguish mild cases from pyorrhœa alveolaris. A method of diagnosis in the early stages, especially in children, was devised by Hess. The arm-band of a sphygmomanometer is placed upon the arm and inflated until the pressure reaches 90 mm., and the venous circulation is shut off. This pressure should be maintained for three minutes and then released. As soon as the cyanosis fades, an examination should be made for the petechial spots which may confirm the diagnosis of scurvy. This test depends on increased permeability of the capillary endothelium. Rotter introduced an intradermal test with dichlorphenol-indophenol.

Differential diagnosis has to be made from blood diseases such as leukæmia, and essential thromboeytopenia (onvalai, see p. 699).

Treatment.—This is chiefly dietetic. The disease, if recognized early, readily yields to a diet composed of fresh fruit and vegetables; when these are unprocurable, fresh meat can be substituted, but is by no means so satisfactory.

Raw onions are very valuable antiscorbutics, and raw potatoes and swedes have a definite curative value. Canned vegetables, except canned tomatoes, are useless.

For natives, the most valuable antiscorbutic foods are orange, lemon, and pawpaw juice, sweet potatoes, and green mealies. Incompletely fermented beer, such as the Kaffir beer, made from germinating grain, is said to be of considerable value, but this is doubtful.

Vaughan, Hunter and others reported brilliant successes in the treatment of scurvy with synthetic ascorbic acid. Many cases were reported by Schultzer, Parsons, Harris, Ray, and Szent-Györgyi; 40–100 mgm. of ascorbic acid are given intravenously to an adult for ten days with success; to infants 30–60 mgm. daily by the mouth for about fourteen days.

Germinating peas are useful when fresh vegetables are unobtainable.

CHAPTER XXIX

KWASHIORKOR

Synonyms.—Malignant Malnutrition, Nutritional Dystrophy. Diboba (Congo). M'buaki (Uganda). Depigmentation-ædème.

The first clinical description of this common tropical disease of children was given in a paper by Procter in Kenya in 1927, but it was Cicely Williams (1933) who, in the Gold Coast, first gave it its distinctive name and described its pathology. The name is derived from the African Ga language and signifies "red man or boy" which denoted the pigmentary changes in the hair. This syndrome appears to be similar to Mehlnühr-



Fig. 63.—Kwashiorkor: œdematous form in a Fijian child of two years. (P. E. C. Manson-Bahr.)

schadung, a starch or flour dystrophy, originally described in Vienna by Czerny and Keller in 1906.

It is definitely a nutritional disease which leads to damage to the liver, pancreas and, indeed in lesser degree, to all the intestinal organs. The main signs and symptoms are cedema, hypoalbuminæmia, hair changes, skin changes—diffuse depigmentation, rashes with hypopigmentation, dermatoses of external genitalia, fatty diarrhœa, mental changes, lack of resistance to cold, anorexia and stunted growth.

Kwashiorkor does not appear to be caused by a single food factor, but by multiple deficiencies. Hence the association with well-known vitamin deficiency is comparatively common. Seasonal alterations in food supply may alter the pattern of the deficiency so that seasonal incidence has been noted wherever the disease

occurs. In the West Indies the incidence is greatest from January to April. In the original descriptions it was emphasized that the disease was quite distinct from pellagra, but subsequently there were some doubters who thought it might be a form of "infantile pellagra." The age varies in children from six months to four years with a high mortality sometimes of nearly 90 per cent. and it is found in neglected children especially after weaning, although Gelfand has described one in a breast-fed infant in Rhodesia. Kwashiorkor occurs mostly in ill-nourished children in the late breast-feeding, weaning and post-weaning ages. He has produced some evidence that it is not due so much to lack of proteins, as to a peculiar staple cereal diet.

Geographical distribution.—Although the original cases came from West Africa, it was soon recognized by Waterlow in the West Indies, in Kenya (an excellent account has been written by M. Clark (1951) in E. African Med. Jl., 28, 6, 229, and by J. F. Brock and M. Autret Bull. W.H.O., V., i, 1-71, and East Africa in general, Rhodesia, S. Africa, Egypt. India (Hare), Indonesia (Oomen), Brazil, Fiji (P. E. C. Manson-Bahr). The pathology of the disease has been well described by Trowell, Gillman and Gillman, and also by Davies in S. Africa.

Pathology is characterized by an enlarged fatty liver, necrotic foci in the pancreas and atrophy of the acini resulting in declining of the enzymatic activity of the duodenal contents. The fatty infiltration of the liver progresses from the periphery to the centre of the organ: recovery proceeding in the reverse direction. Early fibrosis is sometimes present and may lead to lobular and multilobular cirrhosis. Hepatic cirrhosis of this nature is comparatively common in Africans, whilst Waterlow in Jamaica has recorded it in a sixteen month old infant. According to workers in Africa protein deficiency can produce irreversible damage in the liver which leads to fibrosis and eventually to carcinoma of the liver.

Pancreatic changes have been observed by several workers (Gillman and Gillman, Hartz, Davies), but the pancreatic fibrosis described by the latter in adults is not seen in infants.

It has been pointed out that those organs most active in handling protein are also most vulnerable to protein deficiency. These are the pancreas, intestinal tract, liver and salivary glands in all of which lesions have been described. Much of the protein utilized by the gut, pancreas and salivary glands goes to the formation of digestive enzymes, the production of which is known to be impaired by fatty liver disease.

Clinical picture is that of a very sick, cedematous, undernourished child with depigmented scaly skin, with painful sores at the mucocutaneous junctions, mentally, bodily stunted with diarrhea.

Hair changes (Achromitrichia) are almost a constant feature, but most variable. The hairs are scanty, straight, silky to the touch, having lost their normal curl. The colour is greatly changed and may be almost white with a reddish tinge. These colour changes are usually greatest at the sides and back of the head and least on top. The eyebrows are often absent. The changes in the hair are the last to return to normal during recovery. It takes months for the normal colour, texture and curl to be restored. Hughes in Lagos believed that achromitrichia is due to deficiency of pantothenic acid. Administration of this vitamin seemed to restore normal colour.

Skin changes.—Although often most marked this may be slight or absent. The skin changes may be divided into loss of pigment and dermatoses. The characteristic pigment change results in a pale reddishbrown colour, and is most easily noticed on the face where there is a tendency to circumoral depigmentation. Various forms of dermatoses are most numerous. The rash is usually localized at the extensor side of the

extremities and, when peeling off, leaves a depigmented, often reddish, oozing surface, which cracks and is known as "crazy-pavement" skin (Fig. 64). In severe cases it is well marked over the legs, and in mild ones it is best seen over the lumbar region. There is a tendency for the skin to break down, subcutaneous septic abscesses form, giving rise to deep necrotic ulcers of the skin, indescribable damage (as in the Fijian cases) and eventually to keratomalacia and blindness. Gangrene of the limbs may ensue also.

Œdema shows periodic variation. Those with the most marked ædema are invariably fatal. Sometimes it is confined to slight pitting of the legs.

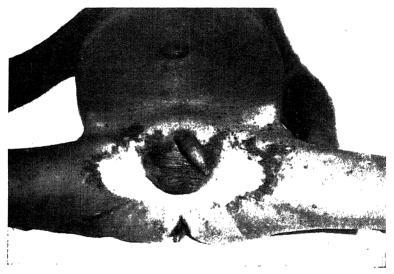


Fig. 64.—Kwashiorkor in a Fijian male child of two, showing characteristic dermatosis, depigmentation and hyperpigmentation. (P. E. C. Manson-Bahr.)

At others the child may be blown up with massive swelling of the eyelids which block the eyes (Fig. 63). The ædema is sometimes deceptive and the child looks fat and plump. At others again he is a wizened little oaf with sunken cheeks, pot-belly and spindly legs. At this stage with proper feeding he may recover.

The ædema may disappear entirely and then return.

Diarrhæa occurs at some time or other in every case, but may be intermittent. The stools are fatty, soft, semifluid and offensive. The steatorrhæa may be so pronounced as to resemble the stools of cæliac disease or sprue. An attack of diarrhæa may be the prelude to a fatal relapse. In these diarrhæa cases the liver is always enlarged, and the liver edge may be palpable, jutting down below the costal margin.

Mental changes.—The kwashiorkor child is dull, apathetic and miserable. It rarely screams or cries, but gives rise to a low and miserable whimper.

It rarely resists examination and never fights or screams. It is pointed out that when a smile appears on the face the child is on the way to recovery.

Lack of resistance to cold.—Even in hot weather these children are cold and need woollen jerseys and thick blankets to keep them warm. When the child is most sick it lies curled in the feetal position.

Anorexia is constant and is most marked in severe cases. It is most

important as the child starts to improve as the appetite reappears.

Stunted growth.—The fact that this disease retards growth makes it difficult to estimate the correct age, which is usually underestimated. The oldest child observed in Kenya was seven, but this is exceptional. Here the Kikuyu, as also the Fijians, wean their children late, sometimes after full dentition has been acquired. In general it may be said that kwashiorkor arises just after a child is weaned, or in children who are late or partially weaned. The mortality in African children is never less than 30 per cent.

As compared with European growth charts there is divergence. Whereas the weight is much the same for the first nine months, from then onwards the curve shows the maximum retardation from the second to fourth years and does not catch up to these standards by the end of the fifth year (Trowell).

Diagnosis.—Clinical pathology.—There is usually difficulty in obtaining blood for investigation from cedematous infants and this is best obtained from the external jugular vein.

Serum proteins.—The average total protein is 4·7 and the mean serum protein content is about 4·2 grm. per cent. The albumin-globulin content when the average total protein is 4·17 is 52 per cent. albumin and 48 per cent. globulin. Trowell and others confirm that there is an increased globulin level.

Liver function test with bromsulphalein shows that most patients have a

value below 10 per cent.

Blood counts.—The mean hæmoglobin content is 9 grm. per cent., corresponding to 3.15 million erythrocytes per c.mm. with MCV of 110

per c. μ with MCHC of 25 per cent.

Bone marrow biopsy reveals a true megaloblastic bone marrow, and a reticulocyte response follows folic acid treatment. Trowell has described macrocytic-hyperchromic (dimorphic) anæmia as the common form. This macrocytic tendency may be considered as evidence of deficiency of the vitamin B₂ complex.

Liver biopsy confirms the fatty infiltration of the liver in grades I

and II.

Faces.—Most have steatorrhoea and the mean total fat is determined as

30-40 per cent.

Kwashiorkor has to be distinguished from hunger ædema, infantile pellagra and cæliac diseases.

Treatment.—The essence of treatment is feeding. No amount of vitamins will cure kwashiorkor. It is protein that these children need. Maize meal must be avoided. If possible the protein is best supplied in

KWASHIUKKUK

Clark claims the best food is minced meat mashed up with ables, soup and milk, but owing to the extreme anorexia, feeding is easy as might appear. The best all-round food for smaller children is milk when it can be procured. Dried milk preparations are not so satisfactory. The Gilmans have obtained remarkable results powdered hog's stomach (10 grm. daily for 10 days). It produces ation of fat from the liver with increased diuresis in 24-28 hours ie with dried stomach is also recommended. Blood transfusions l. per kg.) into the jugular vein are repeated every day or every other r a week or longer. This helps to build up the protein content and air the colloid osmotic pressure which is so important in the reduction edema. It is generally agreed that return to normal dietary should tponed till all symptoms have disappeared, and until the liver is no palpable. The experiences of Van der Sar in Curação have conhim that too early administration of cereals with a mixed diet of d potatoes and vegetables results in a return of the diarrhea. as and biscuits of dextrinized flour mixed with whole milk are the cticles of solid food to be permitted. Cod-liver oil is recommended ıya. The weight curve and the consistency of the stools form the mportant guides.

Il elevations of temperature are usually due to respiratory infections e best combated by injections of penicillin. Extreme ædema occurs assu with muscular wasting; therefore, all patients responding to ent lose weight in the first few weeks.

y infiltration of the liver is always fatal in patients who are not l in time. If it advances to a certain degree the changes are sible. Damage to the liver is usually such that, even when the appears to recover, this organ is impaired in adult life. In Africa it idered that cirrhosis and carcinoma of the liver may be due to fatty tion in childhood.

ial background.—In Curação 55 per cent. of kwashiorkor patients children of unmarried mothers. The same holds good in Fiji, even nen who have disobeyed the tribal law that pregnancy must be d when the child is on the breast. In the West Indies and in Africa ber of cases come from homes where there are seven or eight other n.

Section III.—ABDOMINAL DISEASES

CHAPTER XXX

INFANTILE CIRRHOSIS OF THE LIVER

A SPECIAL type of liver cirrhosis in Indian children was first described by Sen (1887). The disease appears to be peculiar to India, though similar cases have been reported from Mexico, Jamaica and North China. Cirrhosis of the liver of unknown ætiology is widespread in young adults in the tropics, especially in the East Indies.

This disease is prevalent in Hindu children. In Calcutta, from 1891 to 1893 inclusive, infantile biliary cirrhosis—the name given to the disease—caused 1.748 deaths. Although the Hindu and Mohammedan populations of that city are about equal, as many as 1,616 of the deaths occurred in Hindus, whilst only 80 occurred among Mohammedans, the balance of the mortality being among the Eurasians and other races. The disease occurs principally in children under one year, rarely attacking those over three years. K. Rao (1941) stated definitely that it most commonly occurs in children between the ages of six and twentyfour months, that it is not found in Moslems or Europeans, and that it occurs chiefly in vegetarian families. As a rule, it begins during dentition, or about the seventh or eighth month, running a fatal course in from three to eight months. In rare cases it may commence within a few days of birth. Instead of lasting several months, its progress may be much more rapid, and terminate in death in from two to three weeks. In India it is common in Bengal, Madras, Bombay Presidency, and the United Provinces; it is more prevalent in rural districts than in towns.

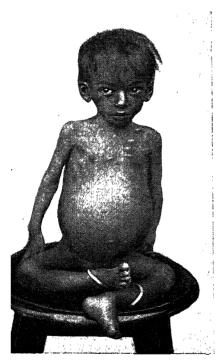
Ætiology.—The cause of infantile cirrhosis is unknown. Neither alcohol, syphilis, nor malaria has anything to do with it. The children of the well-to-do are relatively more frequently attacked than those of the poor. It tends to run in families, child after child of the same parents succumbing within a year or two of birth. Mukerji remarked that the disease is especially apt to occur in grossly overfed and pampered children in Bengal, and has adduced evidence that the virus is probably conveyed by the mother's milk to the child. Green-Armytage believed the true ætiology to be a deficiency of vitamins in the mother's diet, thus depressing the mammary secretion and the endocrine system of the fœtus, in overfeeding of the child when born, and insufficient feeding of milch animals. K. Rao, who isolated Bact. coli from the liver and ascitic fluid, believed that the essential factors are cow's milk and the toxins of Bact. coli. In favour of this hypothesis, he found that the substitution of modern infant milk foods for cow's milk prevents the occurrence of further cases in cirrhosis families. One critical instance is cited of mixed twins in which the female on cow's milk developed cirrhosis, whilst the breast-fed male escaped. Himsworth and Glynn (1944) have described two types of dietary cirrhosis; in the first the fibrosis is diffuse, following fatty infiltration and is caused by choline deficiency; in the second it is coarse, follows massive necrosis and is caused by deficiency of sulphuramino-acids. There also appears to be some evidence that cirrhosis of the liver in childhood may be the sequel of fatty liver disease of malignant malnutrition or kwashiorkor.

Pathology.—Gibbons gave an elaborate and most careful account of the pathological anatomy of this disease; he concluded that it is a peculiar form of biliary cirrhosis, the consequence of the action on the liver-cells of some irritant of gastric origin, which leads to degeneration of the cells in the first instance, with subsequent increase of intercellular connective tissue and, later, of the portal

INFANTILE CIRRHOSIS OF THE LIVER

s. The formation of new bile-ducts between the hepatic cells, which is a arked feature, he regarded as evidence of a natural curative effort, having object a regeneration of the liver-cells. Green-Armytage called the disease llular hepatic cirrhosis. R. Rao (1935) contributed the most profound up to date by the application of the silver impregnation method. He ded that the disease is a subacute toxic cirrhosis. On the other hand a Rao thinks that it is similar to Lænnec's or portal cirrhosis. He sizes the varying degrees of necrosis of the liver cells, the avascular actions connective-tissue network, and the obliterative lesions of the terminal me of the bigger divisions of the hepatic venous tree without appreciable in the portal and biliary trees. There is also a poor attempt at regenerative hepatic parenchyma.

optoms.—Commencing insidiously, the characteristic initial enlargement of er may have made considerable progress before the disease is suspected, course of one or two months the liver has enlarged to the iliac crest. It is smooth and hard, and in some



5.—Advanced case of cirrhosis of the liver ascites and cedema of the hands and feet, no jaundice. (After Krishna Rao.)

cases also, the spleen is hypertrophied. Nausea, occasional vomiting, sallowness, feverishness, constipation, anorexia. irritability of temper, thirst. and languor call attention to the child's condition. Fever of a low type sets in; the sallowness deepens into profound jaundice; the stools are clay-coloured; the urine is dark with bile, and there may be a terminal ascites, with puffiness of the feet and hands. (Fig. 65.) The skin may be bronzed almost as deeply as in Addison's disease. In five months from the onset, ascites and ædema of hands, feet and evelids appear, and in the terminal stages (8-10 months) gastrointestinal hæmorrhages are found. Sooner or later, death from cholæmia ensues. leucocyte count varies from 14,000 to 50,000 in the terminal stages, the increase being due to lymphocytes. accompanying anæmia microcytic.

Diagnosis.—For scientific diagnosis of various forms of tropical liver cirrhosis the method of aspiration liver. In joundiced patients vita-

should be introduced (Sherlock, 1946). In jaundiced patients vitashould be given for three days before the puncture is made (5 mgm. ilon" by the mouth three times daily). With the patient lying with the right arm behind the head, a firm pillow should be placed

under his left side to tilt his body slightly to the right. The cannula of the aspirator is 15 cm. long and 1 mm. in bore, is fitted with a handled trocar and a 20 ml. "record" syringe is used. The puncture is made in mid-axillary or anterior axillary line in the ninth or tenth intercostal space. The skin, pleura and liver capsule are infiltrated with 2 per cent. procaine. The trocar and cannula are passed through the skin and the patient instructed to take a deep breath to displace the lung upwards. The trocar and cannula are passed $\frac{1}{2}$ in. into the liver, the former is then withdrawn and the cannula pushed in a further 4–5 cm. to punch out a cylinder of liver tissue. The syringe is then attached and suction maintained whilst the cannula is withdrawn. The liver fragment is usually found in the barrel of the syringe. If there are any signs of hæmorrhage a blood transfusion must be given. Difficulties may arise in hepatic cirrhosis with much ascites. The risk of hæmorrhage is greatest in severely jaundiced patients. The information obtained from sections is reliable and sections of 10–20 liver lobules may be cut from the piece removed.

Treatment.—According to Green-Armytage, when cases are seen early and parents are given the necessary instruction, recovery takes place in six to ten weeks. Whenever possible, in a family in which several cases of this disease have already occurred, the latest baby should be immediately removed from the mother and artificially nursed and fed upon milk-foods such as Glaxo, Cow and Gate, Ostermilk and Nestlé's foods. Protein hydrolysate (casein hydrolysate) is given in doses of 2-4 teaspoonfuls daily; oranges and tomatoes supply vitamin C; small quantities of rice are well tolerated. Choline is administered in a mixture 15-20 gr. per dose three times daily.

Prophylaxis.—The mother must be fed properly in the antenatal and nursing periods. When weaning begins, the child should be fed on specially prepared infant foods, and 2-3 oz. of fresh fruit should be given daily; iodized salt (iodosol) should be added to all food, as vegetables in Bengal are deficient in salts.

CHAPTER XXXI

CHOLERA

Synonym.—Cholera Asiatica.

Definition.—Cholera (Volupoua = flow of bile) is an acute, infectious, epidemic disease, characterized by profuse purging and vomiting of a colourless watery material, by muscular cramps, suppression of urine, algidity and collapse, the presence of the cholera vibrio in the intestines, and by a high mortality.

Geographical distribution.—It is probable that from remotest antiquity cholera has been endemic in Lower Bengal and in Central China, and has from time to time spread as an epidemic over India. In 1817 it began to extend all over Asia, eastwards as far as Peking and Japan, southwards to Mauritius, and westwards to Syria and the eastern shores of the Caspian. Stopping short at Astrakhan in 1825, it did not on that occasion invade Europe. Since 1830, when cholera first visited Europe, there have been at least five epidemics—1848–51, 1851–55, 1865–74, 1884–86, and 1892–95. Minor epidemics have occurred in Europe since, but have been restricted. During the Balkan War of 1913, and in the course of the 1914–18 war, especially in the Balkans and in Iraq, there were many outbreaks of cholera, but the disease did not extend as an epidemic beyond the actual seat of war.

The 1870-73 epidemic practically spared Great Britain, but it crossed the Atlantic and, entering by way of Jamaica and New Orleans, raged for a time in the United States.

From a study of the march of these epidemics it is to be concluded that cholera reaches Europe by three distinct routes—(1) via Afghanistan, Persia, the Caspian Sea, and the Volga valley; (2) via the Persian Gulf, Syria, Asia Minor, Turkey in Europe, and the Mediterranean; (3) via the Red Sea, Egypt, and the Mediterranean.

Epidemiology and endemiology.—Cholera follows the great routes of human intercourse, and is conveyed chiefly by man—probably in its principal extensions by man alone—from place to place. In India, during religious gatherings, hundreds of thousands of human beings are collected together under highly insanitary conditions, as at the Hurdwar and Mecca pilgrimages. Cholera breaks out among the devotees, who, when they separate, carry the disease along with them as they proceed towards their homes, infecting the people of places they pass through. The Hedjaz has, for the last 100 years, been the point of relay of cholera in its progress from the Far East towards the West. During that period there have been more than 27 outbreaks. In India cholera appears to spread from its home in Lower Bengal over the northern and western, central, and southern provinces in a series of waves of two to four years' duration. Cholera never travels faster than a man can travel; but in modern times, owing to the increased speed of locomotion and the increased amount of travel, epidemics advance more rapidly and pursue a more erratic course than they did eighty years ago. On the other hand, isolated countries, such as the Andaman

Islands, Australia, New Zealand, the Pacific islands, the Cape Province, and the West Coast of Africa, have so far escaped. An epidemic of considerable virulence occurred in Celebes (Dutch East Indies) in 1938 and exhibited several peculiar features. Cholera broke out in Bengal in 1947 and in the autumn months an epidemic of considerable proportions raged in the Delta of Egypt. Centres of less importance are Burma and the Philippines.

Truly endemic cholera centres are found in Lower Bengal and in the Yangtse Valley, China. According to Taylor, an endemic area is:—

(a) one in which the total number of months with absence of cholera deaths does not exceed 30 in 32 years;

(b) one in which a break of five or more months in cholera incidence does not take place.

There are two types of outbreak of cholera, according to whether the general water-supply is contaminated or contamination is localized to certain wells, cisterns, etc. In the former instance the outbreak is explosive and cases occur simultaneously in all parts of the city and disappears again with almost equal suddenness. In the Hamburg epidemic of 1892, during a period of only two months, cholera attacked 17,000 persons, causing 8,605 deaths in a population of 600,000. The water-supply of Hamburg was taken directly from the river, while the adjoining city, Altona (population 140,000) filtered its water from the river by a slow sand process. Although Altona lies further down the river and is contaminated with the sewage of Hamburg, yet the deaths in Altona were only 2.1 per mille as against 13.4 per mille for Hamburg. To illustrate the second type of transmission, there is the well-known incident of the Broad Street pump in 1854. This was the first definite proof of the association of cholera with water. It was noted that cholera was ten times more prevalent in Golden Square than in other parts of London, and increased in the neighbourhood of the Broad Street well. The employees of a factory where the well water was used had a large number of cases, while an adjoining brewery which had a well of its own did not furnish a single case.

Rogers believed that the condition necessary for the spread of cholera in India is an absolute humidity of over 0.400, and that by watching the climatic conditions which influence the seasonal and annual incidence of cholera, increased or epidemic prevalence should usually be foreseen in time for steps to be taken to lessen its spread.

The forecasting of cholera epidemics has therefore become an actual possibility. Based upon statistics which have been subjected to modern scientific analysis, an outbreak can be predicted two to three months ahead. All the co-efficients of correlation between the measure of cholera incidence and other variables to the highest order have been taken into consideration. The association of high relative humidity with high temperature, accompanied by intermittent rains, forms the most favourable atmosphere for the development of the disease, and the presence of endemic centres, from which epidemics may at any time spring, must also be accepted. Indian observers have recently found, on analysis according to the periodogram method, that in South India cholera occurs in a periodicity of six years.

In endemic areas temperature and absolute humidity are the main determining factors. In Bengal in January, when the absolute humidity is low and the temperature relatively so, cholera is at its lowest ebb. As the temperature rises, so does the cholera incidence until May or June when the monsoon sets in; then the humidity rises, but the temperature falls, though it shows a minor rise in October as the monsoon subsides. Wei, in applying the principles of forecasting epidemics in Shanghai, found that cholera tends to occur only when the absolute humidity exceeds 10 mgm. Hg. The combined study of periodicity of epidemics and humidity renders forecasting of epidemics possible.

There appears to be little difference in the susceptibility of different races in the population. Relatively fewer children than adults contract cholera, but they are susceptible and usually the disease runs a severe

course in them.

D'Herelle made the interesting suggestion that the rise and fall of epidemics of cholera may be due to the amount of bacteriophage produced.

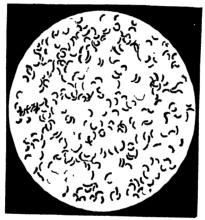


Fig. 66.—Cholera vibrio. Agar culture: 24 hours' growth. × 1,000. (Muir and Ritchie.)

Patients in whose stools no bacteriophage appears die of cholera. cases in whom bacteriophage is strong from the outset, rapidly recover.

Ætiology. Discovery of the comma bacillus, or vibrio.—The cholera vibrio was first discovered by Koch in Egypt in 1883; this discovery he confirmed in Calcutta in 1884 by finding it in every case of the disease examined. His observations have since been abundantly confirmed. Rogers has recently recounted that in India Surgeon-Major Macnamara suggested that cholera was due to living organisms spread by water many years before Koch.

Description of the cholera vibrio.—The comma bacillus (Fig. 66) is a very minute organism, 1.5 to 2 μ in length by 0.5 to 0.6 μ in diameter—about half the length and twice the thickness of the tubercle bacillus. It is generally slightly curved like a comma; hence its name. After appropriate staining, flagella can be distinguished at each end or at one end only—sometimes one, sometimes (though less frequently) two. These flagella, though of considerable length-from one to five times that of the body of the bacillus-are difficult to

see in ordinary preparations owing to their extreme tenuity. They are not always present during the entire life of the parasite. They impart very active spirillum-like movements. The individual bacilli, when stained, show darker parts at the ends or at the centre. Sometimes in cultures two or more bacilli are united, in which case an S-shaped body is the result; or several bacilli may be thus united, producing a spirillar appearance.

The comma bacillus is easily stained by watery solutions of fuchsin, or by Löffler's method, dried cover-glass films being used. It is decolourized by Gram.

The bacillus grows best in alkaline media at a temperature of from 30° to 40° C. Growth is arrested below 15° or above 42° C.; a temperature over 50° C. kills the vibrio. Meat broth, blood-serum, nutrient gelatin, and potato are all suitable culture media. It multiplies rapidly without curdling in milk; it dies rapidly in distilled water; it survives longer if salt be added to the water—for instance, 285 days in sea-water.

In gelatin plates it grows readily as minute white colonies, irregular in shape, and granular, with surrounding liquefaction, into which the colonies of vibrios sink as into funnel-shaped depressions. In gelatin stab-cultures the growth at first is most active near the surface; later, as growth proceeds along the needle track, a finger-shaped liquefaction results, which in time extends to the sides of the tube. In older cultures involution forms are common; they may die out after five or six weeks.

Agar is not liquefied, and in it cultures retain their vitality longer. On potato, at 20° to 30° C., the culture appears as a thin, brownish, porcelain-like film. In broth some of the bacilli form a scum on the surface; others, falling in masses to the bottom, leave the body of the liquid clear. As a rule, the cholera vibrio does not produce hæmolysis, if blood be added to the medium such as agar, after twenty-four hours' incubation. The test is best performed in a fluid medium by adding varying amounts, from 1 ml. downwards, of a three days' culture in alkaline broth to 1 ml. of a 5 per cent. suspension of goat's corpuscles, and then thoroughly mixing. After incubation for two hours the tubes are placed in the ice-chest overnight and read the next day. With the solutions of sugars (1 per cent.) usually employed, the vibrio produces acid, without gas-formation, in glucose, mannite, saccharose, and maltose. Fermentation of lactose, with acid production, occurs two or three days later. The cholera-red reaction is obtained by the addition of pure sulphuric acid to a culture in 1 per cent. peptone solution.

Felsenfeld and co-workers recommend Aronson's medium as the most suitable for isolation of the true cholera vibrio in the following stages:—

- (a) Streaking two plates each of alkaline azar and Aronson's medium directly with stools.
- (b) Inoculation of one tube each of alkaline selenite F and Gohar's alkaline peptone broth with the fæces.
- (c) Incubation of the plates and tubes for twenty-four hours.
- (d) On the second day streaking from the tube to an alkaline agar plate and Aronson's medium.

The true cholera vibrio belongs to Heiberg's Type I, and ferments mannose and saccharose, but not arabinose. It gives positive cholera red and negative Voges-Proskauer reactions; but does not produce early hæmolysis of erythrocytes. These characters alone, however, are not enough for more than presumptive identification, since some non-pathogenic vibrios have most of them. The true cholera vibrio is agglutinated by serum prepared against the O variants of Ogawa and Inaba strains, and this is the principal means of differentiation (Gardner and Venkatraman).

These two strains have now been isolated from the waters of the Hooghly. Panja and Ghosh have shown that brilliant green, malachite green, crystal and methylene violets have a selective bactericidal action in vitro on these two subtypes of V. choleræ.

Until recently a considerable amount of hesitation was felt by many authorities in accepting the cholera vibrio as the true germ-cause of cholera.

Certain organisms, known as the paracholera, or inagglutinable vibrios (Finkler. Prior and El-Tor), resemble the cholera vibrio minutely. Organisms found in fowl cholera, in decomposed cheese, and in river water also resemble it very closely, but, as they behave somewhat differently in the serological sense, they must be considered biologically distinct. Cultures of cholera vibrios have been swallowed many times by way of experiment, and, although in some instances diarrhea has resulted, in only one case has true cholera been produced. Probably for the production of cholera several conditions are necessary, of which the comma bacillus is only one. Gastric acidity is an important factor in determining infection. When vibrios are ingested they are instantly killed in undiluted gastric juice. The difficulty of producing true cholera in lower animals by the administration of cholera cultures has exercised the minds of many, especially in the days following Koch's discovery, but more recently cholera-like symptoms have been produced in ground-squirrels by administering cultures of the organisms in alkaline media.

The exact significance of the non-agglutinating vibrios still remains a matter of debate. Doorenbos brought forward evidence that the El-Tor vibrio and other vibrios which behave somewhat differently are, in fact, the true cholera vibrio contaminated with bacteriophage. Formerly the association of epidemic cholera with a hæmolytic El-Tor vibrio was not considered possible, but de Moor and others in 1938 found that the epidemic in Celebes was caused by a typical El-Tor vibrio as shown by its cultural and serological characters. This vibrio belongs to Gardner and Venkatraman's subgroup O, Heiberg's type I, and is hæmolytic to goat cells. The domestic fly is an important factor in determining the establishment of infection.

Classification of vibrios.—Briefly stated, two main groups of vibrios are recognized:—

Group A.—Cholera and cholera-like vibrios.

Group B.—Other vibrios.

The vibrios in these two groups are morphologically similar, but biochemically and serologically distinct. Those of the latter group are less active fermentatively. but those of the former group are comparatively homogeneous. They have a common H antigen, but a number of O antigens which divide it into many subgroups. The important are in O sub-group 1, which includes the true nonhæmolytic cholera vibrio and the hæmolytic El-Tor vibrio. Thus the true cholera vibrio is non-hæmolytic and agglutinated by pure O antisera prepared by means of the dried heat-stable O antigens of the Inaba and Ogawa sub-types. In India the hæmolytic El-Tor types have not been associated with outbreaks of cholera; in Celebes, in particular, they have been predominant and the only suspected organisms isolated from epidemics with all the classical features of cholera. There is a group antigen common to all the strains of V. cholera (known as antigen A). Ogawa and Inaba strains, in addition to A, have antigens B and C respectively. Other antigens D to M have also been detected. B and C may be present in agglutinable vibrios. For the preparation of vaccines all antigens must be present.

Bacteriophages.—About 13 races of bacteriophage which lyse the cholera vibrio have been isolated. They are known as A-N. Two of these only, A and N, are selecting and act when the cholera vibrio act

are selective and act upon the true cholera vibrio only.

Toxins.—Filtered cultures of the cholera vibrio have little toxic action, the virus being apparently liberated by disintegration of individual organisms. Dead cultures, given by the mouth, produce no effect, unless the intestinal epithelium is injured. The toxins are mostly destroyed at 60° C.; when ground up and frozen by liquid air, an extract of high toxicity to laboratory animals, especially when injected intravenously, is obtained. The organism multiplies in the small intestine, and liberates an endotoxin which is responsible for desquamation of the epithelium and other manifestations of the disease.

Phan was able to produce the clinical phenomena of cholera in guinea-pigs by injecting cholera endotoxin in doses of 0.05-0.1 c.c. in the neighbourhood of the splanchnic nerves. Similar results were obtained in rabbits by injecting doses of 0.2 c.c.

Vibrios do not apparently produce any exotoxin. The endotoxin results from the destruction of vibrios within the bowel lumen. Burrows has shown that it is probably a phospholipid which can increase intestinal permeability without producing any detectable changes in the mucosa. Burnet and Stone have described a mucinase, a tissue-disintegrating substance, in cholera vibrio filtrates.

Methods of infection.—Infected material is conveyed from sick to healthy persons, either by water, food, flies or infected linen. Milk, raw fruit, such as dates in Egypt in 1947, vegetables and other uncooked foods are all able to serve as media for the transference of the vibrio. Clothing, if kept moist, can retain the infectivity for days and weeks. Greig has shown in India that, in stools kept in the dark at room temperatures, the average life of the vibrio is about eight days, but when dried, it only survives for a few hours. In water the vibrios remain viable for a considerable time. In reservoir water they live about two weeks, but some grossly contaminated streams, such as the Ganges, are unfavourable to their survival.

Cholera carriers.—Patients who have recovered from cholera may continue to excrete the vibrio irregularly for a few weeks, but, as a rule, 90 per cent. become free from infection in 14 days and 99 per cent. in a month. The existence of apparently healthy cholera carriers has been recognized, and these may excrete vibrios for two months, though the "carrier state," such as is known in typhoid, does not exist for cholera. Taylor definitely states that the convalescent and contact carriers in most cases are free from the vibrio five days from the onset of the attack or contact.

Immunity.—The guinea-pig or rabbit may easily be immunized against the cholera vibrio by repeated intraperitoneal injections of killed cultures. The serum thus obtained shows marked agglutinative properties in a high titre to cultures of the organism. Furthermore, this serum, when injected into a non-immune animal, has marked protective power against even four or five times the lethal dose. When this happens, active bacteriolysis takes place (Pfeiffer's reaction). The test is performed as follows:

A loopful of a young agar-culture of the vibrio is added to 1 ml. of bouillon containing 0.001 ml. of anti-cholera serum, and is injected into the peritoneal cavity of a young guinea-pig; by means of capillary tubes inserted into the

¹ According to Shousha the maximum period in Egypt (1947) was 42 days.

peritoneum, the peritoneal fluid is examined microscopically every few minutes. If the original culture was a true cholera vibrio, the organisms break up into globules; if not, no change takes place. The inoculation of animals by cholera cultures produces an immune serum which is remarkable for its high agglutinating power, the titre going as high as 1 in 12,000. For an agglutination test to prove that vibrios isolated from the stools are those of true cholera, a serum of a titre of 1 in 4,000 should be used.

Newcomers are more susceptible than indigenous inhabitants, but there is little evidence of acquired herd immunity being produced in the endemic areas, and one attack does not give protection against a subsequent attack.

Pathology.—Rigor mortis occurs early and persists for a considerable time. Curious movements of the limbs may take place in consequence of post-mortem muscular contractions. On dissection, the most characteristic pathological appearances in cholera are those connected with the circulation and with the intestinal tract.

If death occurred during the algid stage, the surface presents a shrunken and livid appearance. All the tissues are abnormally dry. The muscles are dark and firm; sometimes one or more of them are ruptured—evidently from the violence of the cramps during life. The right side of the heart and the systemic veins are full of dark, thick, and imperfectly coagulated blood which tends to cling to the inner surface of the vessels. Fibrinous clots, extending into the vessels, may be found in the right heart. The lungs are usually anæmic, dry, and shrunken, occasionally congested and ædematous. The pulmonary arteries are distended with blood, the veins empty. The liver is generally loaded with blood; the gall-bladder full of bile; the spleen small. Like all the other serous cavities, the peritoneum contains no fluid, its surface being dry and sticky. The outersurface of the bowel has generally a diffuse rosy-red, occasionally, an injected appearance. It contains a larger or smaller amount of the characteristic ricewater material, occasionally blood. The mucous membrane of the stomach and intestine is generally pinkish from congestion, or there may be irregular arborescent patches of injection here and there throughout its extent.

If death occurred during the stage of reaction, the tissues are moist; the venous system is less congested; the lungs are probably congested and cedematous, perhaps inflamed. Very probably there are evidences of extensive enteritis.

Greig has shown that the gall-bladder and biliary passages are frequently invaded by the cholera vibrio and that, as in enteric, this viscus may act as a reservoir of infection. Occasionally, according to the same authority, cholera may be a septicæmia; the vibrios have sometimes been demonstrated in the substance of the lungs and kidneys, and in the spleen.

On miscroscopical examination of the contents of the bowel during the acute stage of the disease the cholera vibrio, in most cases, may be demonstrated. Usually it is in great abundance, occasionally in almost pure culture in the upper part of the small intestine and duodenum, but it may be very scarce in the large gut. Sections of the intestine show the vibrio lying on and between the epithelial cells of villi and glands.

On the whole the vibrios are confined almost entirely to the gastro-intestinal canal, mainly to the lumen. The cholera endotoxins causes a superficial denudation of the epithelium and increases its permeability so that there is great outpouring of water and electrolytes with loss of fluid from the tissues and blood. The tissue changes could possibly be explained by dehydration of the tissues and by hemo-concentration and low blood-pressure, which results in temporary ischæmia.

Bannerjee and Dutta demonstrated focal necrosis in the kidneys with hyaline changes and sclerotic atrophy. There are also marked changes in the convoluted

tubules. On the whole the kidney changes are more in the nature of a nephrosis than of a nephritis.

Symptoms.—Although cholera may declare itself within a few hours of exposure to infection, it may also do so at any time up to ten days. Three to six days may be set down as the usual incubation period. An attack of cholera commences in one of two ways: either it may supervene in the course of what appears to be an ordinary case of diarrhœa, or it may come on suddenly, without any well-marked prodromal stage. During cholera epidemics diarrhœa is unusually prevalent. It is a common observation that at such times an attack of simple diarrhœa may, after a day or two, assume the characters of true cholera. The preliminary looseness in such cases is known as premonitory diarrhœa or cholerine and is, in fact, a mild form of cholera. Besides diarrhœa, other prodromata, such as languor, depression of spirits and noises in the ears are sometimes noted.

Description of the average case.—When true cholera sets in, profuse watery stools, usually associated with griping pains, and at first fæcal in character, pour, one after the other, from the patient. Quickly the stools lose their fæcal character, becoming colourless or, rather, like thin ricewater containing small white flocculi in suspension. Enormous quantitiespints—of this material are generally passed. Presently, vomiting, also profuse, at first perhaps of food, but very soon of the same rice-water material, supervenes. Agonizing cramps attack the extremities and abdomen; the implicated muscles stand out like rigid bars, or are thrown into lumps from the violence of the contractions (due to depletion of chlorides and hypocalcæmia affecting the neuro-muscular junction). The patient may rapidly pass into a state of collapse. In consequence principally of the loss of fluid by the diarrhoea and vomiting, the soft parts shrink, the cheeks fall in, the nose becomes pinched and thin, the eyes sunken, and the skin of the fingers shrivelled like a washerwoman's. The surface of the body becomes cold, livid, and bedewed with a clammy sweat; the urine and bile are suppressed; respiration is rapid and shallow; the breath is cold, and the voice is sunk to a whisper. The pulse soon becomes thready, weak, and rapid, and then after coming and going and feebly fluttering, may disappear entirely. The surface temperature sinks several degrees below normal—to 93° or 94° F.; whilst that in the rectum may be several degrees above normal—101° to 105° F. The blood-pressure is low. The systolic may register 50 mm. of mercury, but is frequently unregistrable. The patient is now restless, tossing about uneasily, throwing his arms from side to side, feebly complaining of intense thirst and of a burning feeling in the chest, and racked with cramps. Although apathetic, the mind generally remains clear. In other instances the patient may wander or may pass into a comatose state.

This, the "algid stage" of cholera, may terminate in one of three ways—in death, in rapid convalescence, or in febrile reaction.

When death from collapse supervenes, it may do so at any time from two to thirty hours from the commencement of the seizure, usually in from ten to twelve. On the other hand, the gradual cessation of vomiting and purging, the re-appearance of the pulse at the wrist, the increase of blood

pressure and the return of some warmth to the surface may herald convalescence. In such a case, after many hours' absence, secretion of urine returns, and in a few days the patient may be practically well again. Usually, however, a condition known as the "stage of reaction" gradually supervenes on the algid stage.

Anuria.—The first signs of anuria are congestion of the mucous membranes and conjunctivæ, malar flush, delirium, and gradual increase in depth and rate of respiration. Recovery is marked by the passage of a few ounces of turbid, highly coloured urine and this is followed by a "critical diuresis" resembling that seen in some cases of acute glomerulo-nephritis.

Renal failure in cholera has been compared to anuria following crush injuries. Tomb claimed that it may be explained by the hypothesis of Freeman that collapse of the circulation, as in surgical and traumatic shock, is the result of over-stimulation of the sympathetic nervous system. This results in dilatation of the capillaries of the skeletal muscles and constriction of the dermal and abdominal vessels. It is suggested that the histological changes in the urinary tubules are due to deprivation of oxygen. The blood urea is invariably raised and may reach 350 mgm. Anuria may persist for 50 hours, and the patient may yet recover. When the patient passes 2 pints of clear urine in 24 hours the danger of relapse has usually passed.

The importance of charting the amount of urine, hour by hour, day by day, in the reactionary stage of cholera cannot be over-emphasized. These data are essential if threatened anuria is to be successfully combated.

Reaction or cholera typhoid.—When the patient enters on this stage the surface of the body becomes warmer, the pulse returns, the face fills out, restlessness disappears, urine is secreted, and the motions diminish in number and amount, becoming bilious at the same time. Coincidently with the subsidence of the more urgent symptoms of the algid stage and this general improvement in the appearance of the patient, a febrile condition of greater or less severity may develop. Minor degrees in this reaction generally subside in a few hours; but in more severe cases the febrile state becomes aggravated, and a condition in many respects closely resembling typhoid fever, "cholera typhoid," ensues. These reactions are due to denuded epithelial lining of the gastro-intestinal tract, permitting the fluid to pass freely so that the toxins are easily absorbed. Acidosis is produced by the failure of the kidneys to excrete them.

During the stage of reaction death may occur from a variety of complications—from pneumonia, from enteritis and diarrhœa, from asthenia, or

from uramia.

Hyperpyrexia is an occasional, though rare, occurrence in cholera. In such cases the axillary temperature may rise to 107° F., the rectal temperature perhaps to 109° F. These cases also are almost invariably fatal.

In cholera there is a considerable variety in the character of the symptoms and in their severity, both in individual cases and in different epidemics. It is generally stated that the earlier cases are the more severe, those occurring towards the end of the epidemic being on the whole milder.

¹ According to Maegraith and the modern school of physiological thought the main factor is renal anoxia (see p. 85).

Ambulatory cases occur during all epidemics, characterized by diarrhœa and malaise merely; there is never complete suppression of urine, the diarrhœa never loses its bilious character, and is not accompanied by cramps. The attack gradually subsides without developing a subsequent stage of reaction.

Cholera sicca.—A very fatal type is known as "cholera sicca." In these cases, though there is no, or very little, diarrhoea or vomiting, collapse sets in so rapidly that the patient is quickly overpowered as by an overwhelming dose of some poison, and dies in a few hours without purging or any attempt at reaction.

Eye changes in cholera.—Osmotic dehydration in cholera can bring about a lens opacity, which, in lesser degrees, is reversible, so far as the physical state of the water in the lens is involved.

Therefore cataract may develop suddenly in the stage of collapse and may have a similar osmotic basis to that of diabetes. In cholera loss of fluid from the bowel may lead to osmotic dilution of the body fluids, including the aqueous, and consequent inflow of water into the lens.

The ophthalmoscopic changes consist of a wavy gridiron appearance with dark lines against a red background, possibly denoting wrinkling of the capsule.

Complications.—The common complications are persisting enteritis, diarrhæa, corneal ulcers, cholecystitis and abortion in pregnant women. Pneumonia is common in the colder countries, but rare in hot ones. Gangrene of the extremities, penis and scrotum, formerly observed, is seldom seen nowadays.

These changes disappear on rehydration.

Clinical pathology.—On account of dehydration there is often a polycythæmia and the red blood count often rises to seven millions per c.mm., with a disproportionate leucocytosis up to 20,000 per c.mm. with a relative mononuclear rise. The sedimentation rate is increased in the great majority of cases and mainly in the serious cases, in which the specific gravity of the blood is high, the sedimentation rate lies within normal limits

With suppression of urine the non-protein nitrogen and urea are raised considerably, but return rapidly to normal. There is great reduction in alkaline and chloride reserve, with resultant acidosis and retention of nitrogenous waste products that further increase renal failure. Thus Bannerjee (1941) showed that in an average case 10 grm. of sodium chloride may be lost in the vomitus and 35 grm. in the fæces within 24 hours.

Delaydration symptoms are mainly due to dehydration and loss of chlorides. The similarity between a patient with cholera and one in shock is great, but in the latter there is a loss of all the plasma elements. The best measure of dehydration is the specific gravity of the blood, which may rise to 1064.

Renal failure.—Hæmoconcentration and circulatory failure through loss of blood volume and toxic vasomotorparesis with resultant hæmostasis will lead to failure of renal circulation. Temporary ischæmia may cause irreversible changes in the kidney.

The urine, prior to suppression, is highly coloured with high specific gravity and a distinct cloud of albumin, but subsequently the first urine passed contains a high percentage of albumin, hyaline and granular casts with a chloride content as low as 0.1 per cent.

Sequelæ are unusual. Recovery is generally complete. Occasionally there are minor sequelæ, such as anæmia, mental and physical debility, insomnia, a diphtheritic inflammation of the mucous membranes of the intestines, fauces and genitalia, nephritis, different forms of pulmonary inflammation, parotitis apt to end in abscess, ulceration of the corneæ, boils, bedsores, and gangrene of different parts of the body. Jaundice occurs at times, and is said to be of the gravest import. An interesting, but unusual, sequel is bradycardia. Pregnant women almost invariably miscarry, the fœtus showing evidences of cholera.

The prognosis of cholera is especially bad in opium addicts.

Diagnosis.—During the height of an epidemic the diagnosis of cholera is generally easy; the profuse rice-water discharges, the collapse, the cold clammy skin, the cyanosis, the shrunken features, shrivelled fingers and toes, the feeble husky voice, the cold breath, the cramps, and the suppression of urine, together with the high rate of mortality, are generally sufficiently distinctive. But in the first cases of some outbreaks of diarrhæa, which may or may not turn out to be cholera, and the true nature of which, for obvious reasons, it is important to determine, correct diagnosis may not be so easy. Control measures should be applied if the clinical evidence is suggestive, without waiting for bacteriological confirmation.

In other forms of diarrhœa it is rare for the stools to be persistently so

entirely devoid of biliary colouring matter as they are in cholera.

The detection of the comma vibrio in the stools is regarded as a positive indication of cholera. It would be rash, however, to affirm that a negative result from bacteriological examination of a single case rules out cholera. Moreover, such examinations, to be trustworthy, have to be made by a skilled bacteriologist.

In the first place the stools should be examined microscopically. If vibrios are present in large numbers they may be detected by their scintillating rotatory movements in hanging-drop preparations, or by their characteristic shape in feecal films stained by carbolfuchsin. Diagnosis may be made:—(a) Inoculate several loopsful of stools into a tube of pentone water (1 per cent. peptone, 0-5 per cent. sodium chloride adjusted to pH 8-4). Incubate for eight hours. Take a loopful and examine fresh or stained for Gram-negative motile vibrios; (b) take a loopful from the peptone culture and streak on Vedder and Van Dam (hæmoglobinpeptone-glycerine and KOH—pH 8·4), Dieudonné, or Aronson plates for 12 hours. Pick out greenish in the first two, or red in the third colonies and confirm that they are vibrios; (c) carry out agglutination tests with standard high-titre and anti-O sub-group 1 cholera serum to exclude all but El-Tor, and true cholera vibrios; (d) in order to show whether hæmolytic (El-Tor), or non-hæmolytic (true cholera vibrio), to a 5 per cent. sheep-blood corpuscular suspension in saline add an equal quantity of vibrio emulsion. Incubate at 37° C. and read after two hours and again after eight hours.

The full technique of identification demands a considerable amount of time, and as promptness is the first essential in cholera diagnosis, be it of acute cases or of "carriers," other methods of rapid and more or less accurate diagnosis have

been devised. Such a one is Bandi's method, which consists in inoculating the suspected fæces into peptone water containing agglutinating serum of such strength as to clump the cholera bacillus in high dilution. Within as short a period as three hours' incubation, agglutination visible to the naked eye is said to be present. This method, when employed in a large number of cases, necessarily consumes a large quantity of immune serum¹.

In an autopsy on a suspected case of cholera at least two sections of the small gut, each about 5 in. in length—one just above the ileocæcal valve, the other in the middle of the ileum—should be ligatured, cut off, dropped into sterile saline and sent to a bacteriological laboratory as soon as possible for examination.

An agglutination reaction is not obtainable from the blood-serum during the acute stage, but it is present after eight to ten days from the commencement of the disease, reaching its maximum in four weeks; it may attain a titre of 1 in 1.000.

Taylor made it plain that the question of H and O agglutinins is important in the diagnosis of cholera, as it is in other intestinal diseases of bacterial origin. The H element is present in some strains of true cholera and also in all the saprophytic water vibrios. It is affirmed that the O agglutinin is all-important. Evidence is accumulating that the O groups of vibrios are responsible for most of the serious outbreaks of cholera. Therefore, it is important that sera from cholera cases should be tested for O agglutinins.

Differential diagnosis.—True cholera may have to be differentiated from *mushroom* poisoning, which may simulate it very closely, but in this instance there is usually a history of several persons having been attacked at the same time. Leucocytosis is absent in food-poisoning though usually found during the early stages of cholera.

Differential diagnosis of cholera from food poisoning is based upon the violent and distressing vomiting which precedes the diarrhoea, the severity of the abdominal pain and the greenish offensive nature of the stools. The urinary flow is never suppressed, whilst the axillary temperature is raised.

Algid or choleraic subtertian malaria may simulate true cholera very closely (see p. 57); acute bacillary dysentery may occasionally be so sudden and severe in its onset as to resemble cholera; acute trichinosis is distinguished by leucocytosis and pronounced eosinophilia; in arsenical or antimony poisoning vomiting, continuous, mucous and often freely streaked with blood, is more usually the most urgent commencing symptom. Children suffering from cholera are apt to develop hyperpyrexia with cerebral manifestations, which may be mistaken for meningitis.

TREATMENT

During cholera epidemics it is customary to establish depots where sedative and astringent remedies for the treatment of diarrhoea are dispensed gratuitously. Chlorodyne in small doses, 10-15 drops, has been found to be of value in allaying the more urgent primary manifestations.

SPECIFIC TREATMENT.—Sulphaguanidine is tolerated in very large doses. That recommended is 0-1 grm. per kilo body-weight, immediately followed by 0-05 grm. every four hours. That is to say that a patient of moderate

¹ According to Shousha in the Egyptian epidemic of 1947 diagnosis was greatly facilitated by taking swabs from the recisum

size—50 kilos or 110 pounds—should receive an initial dose of 5 grm., followed by 2.5 grm. every four hours until symptoms subside. Formo-

cibazol may be more effective than sulphaguanidine (Collier).

Sadusk and Oswald, from studies on bacteristatic and bactericidal action on the cholera vibrio, found that sulphathiazole is more active than sulphadiazine, sulphaguanidine or sulphanilamide, but the latter are more readily absorbed from the intestine and for this reason sulphaguanidine is preferable (though 40 per cent. is absorbed). Lahiri recommends lower doses of sulphaguanidine than stated above. Extracts of suprarenal cortex in the form of eucortone are given intravenously, 2 ml. in 100 ml. of 25 per cent. glucose, followed by saline transfusions.

Kaolin, or "bolus alba," as an adsorbent, has been disappointing. It

consists of kaolin 200 grm. (7 oz.) in 400 ml. of water.

Bhatnagar, Fernandes and colleagues (1948) announce the discovery of a compound, $C_{21}H_{22}O_6N_6S_4$ (compound 6257). In vitro bactericidal action on cholera vibrios is well marked. The compound was originally formed from a condensation product of sulphathiazole and formaldehyde. In the field the drug was given to cholera patients in doses of 6 grm., followed four hours later by 4 grm., usually by mouth or rectum. As a rule the total dosage was 28 grm., of which 10 grm. were given on the first day. The mortality was reduced to 4 per cent. It is said that the drug has also a certain prophylactic effect. Chloromycetin and aureomycin have been favourably commented upon (Gould).

Subsidiary measures.—The patient should be kept strictly in the horizontal position, in a warm bed, and in a well-ventilated, but not too cold room. Thirst should be treated by sips of iced water, soda-water, champagne, or brandy and water. Copious draughts, as they are likely to provoke vomiting, are usually condemned. It does not follow from this that they are harmful; the emesis contributes to the elimination of toxins. Cramps may be relieved by gentle frictions with the hand, by a small hypodermic injection of morphia, or, these failing, by chloroform

inhalations.

The surface heat is maintained by hot-water bottles or warmed bricks placed about the feet, legs, and flanks. The patient must not be allowed to get up to pass his stools; a warmed bed-pan should be provided for this purpose. The foot of the bed should be raised. All food should be withheld while the disease is active.

Maintenance of biochemical equilibrium.—These measures are: (1) Replacement of fluids; (2) Maintenance of blood and tissue chlorides at

their natural levels; (3) The counteraction of acidosis.

Intravenous salines.—For the stage of collapse, which is due to the loss of a large amount of fluid, intravenous injections of salines must be resorted to in order to restore the balance. Collapse in cholera does not differ fundamentally from that due to hæmorrhage, and similar principles of treatment underlie both. Intravenous injection of normal saline is therefore indicated, but success appears to depend on the introduction of a sufficient quantity. Three to four pints may be necessary. Many years ago Cox of Shanghai had encouraging results from continuous, prolonged, slow intravenous injections of isotonic saline fluid given by a

special apparatus placed $2\frac{1}{2}$ ft. above the level of the patient's arm. The flow was kept up for several hours, at a rate of 2 oz. per minute, as long as there was danger from collapse. The modern drip transfusion method is preferable (see p. 859).

The following are the modifications of saline therapy which are

advocated :--

Modified Rogers's treatment.—Pyrogen-free sterile distilled water should be used. (Pyrogen-free water—Add powdered charcoal (B.D.H. activated charcoal) in proportion of 1 grm. to the litre. Shake thoroughly for a few minutes and put aside for charcoal to settle. Keep in stoppered flask.)

(a) Hypertonic saline: Sodium chloride 140 gr., or 16 grm. Distilled H₂O . . to 1 pint, or to I litre (b) Alkaline saline: Sodium chloride . 80 gr., or 9 grm. Sodi bicarbonate . 180 gr., or 20.5 grm. Distilled H₂O . . 1 pint, or 1 litre (c) Alkaline hypotonic saline: Sodium chloride . 60 gr., or 6.8 grm. 180 gr., or 20.5 grm. Sodi bicarbonate Distilled H₂O . . 1 pint, or 1 litre (d) Bicarbonate solution (5 per cent.): Sodium bicarbonate . . . 440 gr., or 50 grm. Distilled H₂O . . 1 pint, or 1 litre

Indications.—During sterilization the bicarbonate tends to be converted into the carbonate, but Sellards found that this tendency was minimized by sterilization in an autoclave connected with live steam at 7 lb. pressure.

Intravenous injections should be given to all cases in which there is dehydration with a systolic blood-pressure below 80 mm. of mercury, or specific gravity of the blood from 1058-1060. Up from 1060 to 1062, 2 pints should be injected; from 1062 to 1064, 3 pints.

It is recommended that hypertonic and alkaline saline should be given in proportion of 2:1 within 24 hours of onset. Later acidosis is apt to develop and then the proportion should be reversed and one part of hypertonic saline with two parts of alkaline saline should be given.

After a further 48 hours acidosis may again become a prominent feature, so that alkaline hypertonic saline should be injected again. If the specific gravity of the blood is not much increased the bicarbonate solution alone is indicated.

When the pulse recovers and the patient complains of oppressive pain in the chest the rate of transfusion should be decreased and given at a rate of 1 pint in 15-20 minutes, but if the rectal temperature is 101° F. or above, all intravenous infusions should be given with caution or hyperpyrexia may occur. In children hypertonic saline may be given subcutaneously, intramuscularly or into the sternum or tibia. Intraperitoneal infusions are contraindicated. During saline infusions, half-hourly charts of the rectal temperature should be kept. Should hyperpyrexia supervene, ice packs must be applied and iced water injected per rectum.

A blood-pressure below 70 mm. of mercury indicates a dangerous collapse, and a specific gravity of the blood of 1063, or over, indicates a loss of half the fluid from the blood. In the acute stage the specific gravity of the blood varies between 1060 and 1072, the normal figure for a European adult being 1058 and for an Eastern native 1056.

The specific gravity of the blood is estimated by employing a series of small bottles of aqueous glycerin with specific gravities increasing by 2° per bottle from 1048 to 1070. The specific gravity may be controlled by a urinometer. Blood from the patient is dropped on to the surface of the fluid in the bottles by a capillary pipette. The drop which remains stationary in the centre of the glycerin solution of a given strength indicates its specific gravity.

In the stage of collapse, anuria often occurs, and every effort must be maintained to re-establish the blood-pressure. Pituitary extract, or pitressin, is often useful during the stage of reaction, given in doses of ½ to 1 ml., hypodermically, two to four times a day. Caffeine citrate, 5 gr., is useful as a cardiac tonic and as a diuretic; it may be given three or four times during the twenty-four hours. Chatterjee (1953) finds that avomine, 25 mgm. (promethazine and 8-chlorotheophyllene), 1-2 tablets, checks the intractable vomiting and so permits the oral replacement of fluid.

Cholera typhoid must be treated much as ordinary enteric fever.

In cholera convalescents the diet for a time must be of the simplest and most digestible character—diluted milk, barley-water or rice-water, thin broths, meat juice, and so forth—the return to ordinary food being effected with the greatest circumspection.

Mortality-rate.—The death-rate for cholera has always been high. In former days in India it was seldom less than 70 per cent. In the decade ending 1908 it was 54·2 per cent. in Indian and 78·5 per cent. in British troops in India. With improved methods of treatment it has declined, but is still about 20 to 30 per cent. The death rate in collapsed cases is considerably higher, and, even with modern methods, remains about 65 per cent. Under hospital conditions at present it is about 10 per cent. In epidemics it is usually found that the death rate is higher at the beginning than at the end of the epidemic.

The prognosis is unfavourable in those over fifty years of age and in children under five.

Prophylaxis. Quarantine prevention.—Theoretically, quarantine should be an efficient protection against the introduction of cholera into a community. Even if the utmost care, intelligence, and honesty succeed in excluding individuals actually suffering from cholera, or likely within a reasonable time to suffer from it, there is yet no guarantee that the germ of the disease may not be introduced. Convalescent patients may pass vibrios in their stools. For the recognition of the carrier state it is necessary to examine the stools of all contacts. A small dose of calomel to clear out the contents of the small intestine greatly increases the chance of recovering the specific organism from stools. This is the only scientific method of conducting a reliable quarantine.

Attention is being given to sanitation rather than to quarantine. During the great religious festivals the sanitary condition of the devotees is looked

after as far as practicable, special care being given to provide them with good drinking and bathing water. On the appearance of cholera in the vicinity of troops in India, special protective measures are promptly instituted, elaborate directions having been drawn up for the guidance of medical officers.

Potassium permanganate is the popular disinfectant for wells. The main advantage lies in its extreme simplicity of application. Its action on cholera vibrios in high dilution appears specific, but the customary criterion of adding permanganate until the water is slightly pink is unsafe. A dilution of 1:500,000, which produces a faint purple colour in filtered water, kills cholera vibrios in a short time. This dilution is obtained by adding $\frac{1}{6}$ gr. of permanganate to each gallon of water, or roughly 1 lb. to each 50,000 gallons. In a well of 1,768 gallons the amount would be $\frac{1}{2}$ oz. Neither permanganate nor bleaching powder should be thrown into the well, but the mixture should be made in a bucket, the supernatant fluid should be poured off until the whole amount has gone into solution, then it should be mixed thoroughly withthe well water by repeatedly lowering and raising the bucket.

General disinfection of water supplies.—For chlorination the usual rule is 1 part in 5 million (chlorine content in bleaching powder is 33½ per cent.), or 6 lb. of bleaching powder per million gallons of water.

In the calculation of the amount of bleaching powder, standard solutions with distilled water are necessary: (a) 1:1.000 solution of powder to be used, (b) 10 per cent. potassium iodide solution, (c) 1 per cent. starch solution.

In order to ascertain the volume of water this can be calculated from the depth of the water and diameter of the well by the formula $\pi r^2 \times \text{depth}$, when r is the radius ($\frac{1}{2}$ diameter) of the well. The capacity of tanks and cisterns is calculated by multiplying the length by breadth by depth of water. One cubic foot of water is equivalent to 6 gallons. For this purpose five white bowls with 500 ml. of water to be treated are necessary.

Take a clean 1-ml. pipette and flush with distilled water. With this pipette add varying quantities of 1:1,000 bleaching powder solution to the water in the five vessels. Mix 0.5 ml., 0.7, 0.9, 1-1 and 1.8 to first, second, third, fourth and fifth bowls respectively. Stir the mixture in each bowl with a clean glass rod, commencing with the bowl containing the least amount of chlorine solution, going to the one containing the next smallest, and so on. Allow to stand for at least one hour. Then test for free chlorine by adding to each bowl about 1 ml. of 10 per cent. potassium iodide solution and 1 ml. of freshly-prepared starch solution. Mix well and into the first bowl that gives a faint blue colour. Note the amount of bleaching powder solution that was added to that particular bowl and multiply by 20. The result gives the number of bowls of bleaching powder required for 1,000,000 gallens of water. To this figure add 3 lb. For example: The third bowl is the first to give the faint blue colour, then $0.9 \times 20 = 18$ lb. + 3 lb. = 21 lb. In the case of a well containing 1,768 gallons of water, the amount would be :-

$$\frac{1,768 \times (18+3) \text{ lb.}}{1,000,000} = 0.087128 \text{ lb.} = 0.260 \text{ gr., or } 17 \text{ grm.}$$

Haffkine's inoculation.—During the 1914–1918 war many millions of anticholeraic inoculations were made. The initial dose is ½ ml. of an emulsion of 4,000 millions, followed seven to ten days later by a second inoculation of 1 ml. containing 8,000 millions. Experience has shown that even larger doses can easily be tolerated. Local reaction is, generally speaking, very mild. There may be ædema and a painful infiltration at the site of the injection, rarely followed by systemic disturbance.

Several strains of cholera vibrios are used. They are inoculated into Roux bottles containing "pea-extract agar" and grown for forty-eight hours. The growth is washed off with normal saline, and the emulsion counted, with dark ground illumination. The emulsion is then heated to 55° C. for one hour, after which 1 per cent. carbolic is added. The emulsion thus sterilized is finally diluted down so as to contain 8,000 million vibrios per ml. of saline and 0.5 per cent. carbolic.

The immunity thus produced does not seem to be very persistent, lasting

at the maximum for three or four months.

Experience, particularly that obtained during the Balkan War in 1913, in Batavia in 1915 and 1916, and in the 1914–18 war, has gone far to confirm the earlier impressions of the value of Haffkine's inoculation.

In India from 1905–1916 the annual number of deaths attributed to cholera was never less than 300,000. Epidemics of cholera are readily controlled by vaccine when inoculation is made compulsory; thus, when this disease was introduced into Korea from China in 1926, the outbreak was promptly brought to a close by the inoculation of more than one million persons.

The outbreaks of cholera in Egypt in 1947 offered an opportunity of estimating prophylactic value of cholera vaccine. It was shown that villages, in which inoculation was carried out before cases of cholera had occurred, showed a lower incidence and case mortality than those in which

inoculation was commenced after the outbreak.

Personal prophylaxis.—During cholera epidemics great care should be exercised to preserve the general health; at the same time, anything like panic or apprehension must be sedulously discouraged. Visits to cholera districts should be postponed, if possible, seeing that the newcomer is especially liable to the disease. Unripe fruit, over-ripe fruit, shell-fish and food in a state of decomposition should be avoided1. All drinking-water, and all water in which dishes and everything used in the preparation and serving of food are washed, should be boiled. Mere chlorination of the water with bleaching powder (CaOCl2), giving 1.3 parts of chlorine per million, or added to water in the proportion of 2 grm. of the powder to every 110 gallons, is not entirely reliable. Sodium bisulphate tablets (2 grm. to 13 pints of water), by liberating sulphuric acid, provide a most useful method of sterilizing water for personal use, as for instance in a water-bottle. Filters—except perhaps the Pasteur-Chamberland—are not for the most part to be relied upon; in many instances they are more likely to contaminate the water passed through them than to purify it. A good plan in a household, or in public institutions, is to provide for drinking purposes an abundant supply of weak tea or lemon decoction, the supply being renewed daily; such a plan ensures that the water used in the preparation of the drink has been boiled. All food should be protected from flies. Diarrhea occurring during cholera epidemics should be vigorously treated.

¹ According to Shousha (1947) the cholera vibrio cannot be recovered from any article of food after a period of three days. In acid citrus fruits it is immediately destroyed.

CHAPTER XXXII

THE DYSENTERIES AND LIVER ABSCESS

Three types of dysentery, correlated to three specific and, zoologically, widely separated parasites, have now been definitely established. Though of a totally distinct ætiology they are not mutually exclusive, for one type may be superimposed upon or complicate another; moreover, any, or all of them, may be implanted on some general disease, such as malaria or typhoid. The term "dysentery" denotes a symptom-complex, but does not indicate any particular disease of distinct ætiology. It is most important that a sane and critical view should be taken on this differential diagnosis of the dysenteries as there are many pathological conditions of the intestines which may give rise to a discharge of blood and mucus, but which are unconnected with any parasitic infection.

The principal forms of dysentery and their respective parasites are as follows:

I. BACTERIAL—

THE BACILLARY DYSENTERIES:

Shigella dysenteriæ—Schmitz, Flexner, Newcastle and Sonne bacilli.

II. PROTOZOAL—

Amœbiasis—Amœbic dysentery, Liver abscess, etc.

Entamæba histolutica.

BALANTIDIAL DYSENTERY: Balantidium coli.

III. HELMINTHIC—

BILHARZIAL DYSENTERY:

Schistosoma (Bilharzia) mansoni, S. hæmatobium, S. japonicum.

VERMINOUS DYSENTERY:

Œsophagostomum apiostomum and Œ. stephanostomum.

I. BACILLARY OR EPIDEMIC DYSENTERIES EKIRI—Japanese

Definition.—Acute epidemic diseases due to invasion of the mucosa of the large intestine by specific bacilli (Sh. dysenteriæ, Schmitz, Flexner, Newcastle or Sonne). Pyrexia, symptoms of toxic absorption, and the discharge of blood-stained mucus in the stool usually occur. In severe cases coagulation necrosis of the mucosa may take place and quickly lead to death. In the milder forms the chinical symptom may be a simple diarrhosa.

Geographical distribution.—Epidemics of bacillary dysentery are frequent, both in the tropics and in temperate countries. At present such epidemics are of greater intensity and frequency in those countries in which insanitary habits and more primitive conditions lend themselves to the spread of disease. In mediæval times bacillary dysentery epidemics seem to have been much more widespread and virulent at a time when the sanitary conditions were more akin to those prevailing among primitive tropical natives. In Europe, bacillary dysentery is mainly an institutional disease, occurring not infrequently in lunatic asylums, prison camps, and military barracks. In the Gallipoli campaign (1915) it was responsible for the majority of the 120,000 medical casualties evacuated at that time. Sonne dysentery has been widespread, especially in children, during recent years, in winter time, in England, Europe and America.

Epidemiology.—In the tropics and subtropics bacillary dysenteries appear to observe a definite seasonal incidence. They are certainly prevalent during the rainy season and for a short subsequent period, but mostly in the autumn months, whilst minor epidemics may also occur in the early spring. During the hot dry African summer they are in abeyance. Epidemic dysentery is associated with the rainy season in the tropics for the following reasons:—The rains deter people from defæcating at a safe distance from the village; waterlogging of the soil prevents the bacilli from dying out; people are more liable to chills, which often cause an acute attack; natives crowd together, a tendency which increases the chances of infection, together with increased risk of pollution of water supplies. The infection, as a rule, spreads rapidly from man to man.

Bacillary dysentery has always been a scourge of war. That bacillary dysentery was the predominating form in every epidemic of war dysentery was pointed out by the Editor and many others. During the 1939–45 world war, though bacillary dysentery was prevalent in the earlier stages in the Middle East, yet it was milder in type and eventually, owing to specific treatment with sulphaguanidine, it became quite unimportant. In the European theatre it was hardly in evidence at all.

Direct contagion by fæces occurs, as a rule, among primitive communities in which the ordinary sanitary observances are either unknown or disregarded. The spread of dysenteries in lunatic asylums and Indian bazaars is attributable to personal habits which lend themselves to dissemination of infection. Contamination of food by the soiled hands of carriers, especially Army cooks, and contamination of vegetables by employment of human nightsoil as a fertilizer are also possibilities to be reckoned with.

Indirect contagion. (a) Flies.—There appears to be little doubt that houseflies (Musca domestica) commonly act as carriers of the infection. The seasonal incidence of bacillary dysentery corresponds in a remarkable manner with the maximum prevalence of these pests. In 1910 the Editor demonstrated Shiga dysentery bacilli, in considerable numbers, in the intestinal tract of houseflies in an endemic area in Fiji. The housefly is able to spread dysenteric infection, firstly by regurgitation preparatory to feeding on food; and secondly (probably more commonly) by its fæces.

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LABLE VII.—UIGIDORIGAL INDACTIONS OF LATITUDING AND MILITAL CANDENSING FOR	DIOTO.	COLORE	PEACE	OFFICE	1411	TOTAL STATE OF THE	THE CHI	1		1					· ;		
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Salmonella enteritidis .	+	+	+	+	+	+	0	0	o	0	+	+	7	+	=	5	+
Bacterium coli	+	+	+	+	+	+	+	+	0	0	+	+	+	5	+	+	+
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A = acid, G = gas, Alk = alkaline, Sl = slight.

* To differentiate S. anteritidis and other organisms of the food-poisoning group from S. paratyphi B. serological tests must be applied.

The importance of the insect in the spread of the bacillary dysenteries can therefore be understood. This work was confirmed by Stewart (1944) who found, in North Africa, that houseflies could carry virulent dysentery bacilli for as long as 11-12 days.

(b) Water acts as a medium of infection, especially in Indonesia and Malay States. It has been shown that the bacillus can survive in drinking-water for over three weeks, but not for long when exposed to

the sun, or when associated with putrefactive micro-organisms.

(c) Milk.—Several outbreaks of Flexner and Sonne dysentery in southern England and in Europe have been ascribed to contaminated milk.

(d) Food.—Sonne dysentery is a food infection and should be classified among the group of food-poisonings. One of the largest outbreaks in

- London in 1933 was ascribed to eating "pease pudding."

 (e) Susceptibility of the individual.—New arrivals in the tropics are liable to this form of dysentery, and small children are specially so. Patients whose resistance has been undermined by intercurrent disease such as malaria, pellagra and tuberculosis, are apt to suffer severely from terminal bacillary dysentery.
 - (f) Carriers (see p. 484).

Etiology.—Shigella dysenteriæ was discovered by Shiga in 1898. confirmed two years later by Kruse in Germany. It has therefore been known on the Continent as the Shiga-Kruse bacillus.

Shiga's bacillus is a rod-shaped Gram-negative organism, 1 to 3 μ in length by 0.4 µ in breadth; it is non-motile, and often exhibits very active Brownian movement. Vedder and Duval have demonstrated numerous lateral flagella of great tenuity. On agar and gelatin it grows as a thin smooth film with regular margins, and on MacConkey plates its colonies much resemble those of the typhoid bacillus; they are regularly round, light-blue and dew-like. It produces no liquefaction of gelatin, and grows as a transparent, almost invisible, laver on potato. With solutions of the sugars (see Table VII, p. 473) it produces acidity in glucose, but is inert in the rest of the series and does not produce indol in peptone water. The organism is agglutinated in high dilutions by the serum of patients suffering from the disease. It occurs in considerable numbers in dysenteric lesions, and in the mucous stools of the corresponding period of the disease.

A variety of Shiga's bacillus (resembling that organism in its sugar reaction, but forming indol and not agglutinating with Shiga-immune serum) is known as Schmitz's bacillus and has been shown to be of considerable importance in the Middle East. (This organism is identical with B. ambiguum of Andrewes.)

Para-Schmitz organisms allied to, but antigenically distinct from, type form small discrete, smooth colonies on MacConkey's agar.

Cultures of Sh. shigæ are toxic to laboratory animals, especially rabbits, but in these animals they do not produce lesions characteristic of dysentery, though filtered toxins, when injected intravenously, cause necrosis of the mucosa of the large intestine. In two experiments in man, one intentional, the other accidental, ingestion of pure cultures was followed, within a short time, by well-marked symptoms of dysentery.

Sh. flexneri (the Flexner-Boyd group).—In 1900 an organism morphologically similar to Shiga's bacillus, but differing in the production of acid from mannite as well as glucose, producing indol from peptone somewhat irregularly, and inagglutinable with Shiga-immune serums, was isolated by Flexner from cases of dysentery in Manila. From the work of Andrewes and Inman on a very large number of strains of Flexner—the mannite-fermenting group—it can be definitely stated that the organism does not adhere to one constant type, as does Sh. shiga, but differs greatly in the toxicity of the various strains and in their antigenic properties. Boyd (1938) in a study of antigenic variation among mannite-fermenting dysentery bacilli suggests that loss in culture of type-specific antigen, which is not shared by other members of the group, is associated with an increase, real or apparent, of non-specific group antigen. It seems probable that available cultures of the historical Hiss and Russell Y are degenerate variants of an original W strain, and that an Indian strain, 103A, is the type-specific Flexner-Y. This has been found to be fairly common, both in the United Kingdom and in other parts of the world (W. M. Scott, quoted by Boyd). This work emphasizes the great importance of using type-specific suspensions in diagnostic agglutination tests. Stock Flexner-Y strains may on these grounds be almost or quite devoid of type-specific antigen.

The Newcastle bacillus, first recognized as a cause of dysentery by Clayton and Warren, corresponds to Boyd's No. 88 (see Table VII). It has now been found in other parts of England, India and Nigeria. Owing to the fact that it forms small quantities of gas in solution of the sugars and is motile on first isolation, it

frequently escapes detection.

Sonne's bacillus (Shigella sonnei), which ferments lactose slowly, is responsible for outbreaks of enterocolitis in Egypt and elsewhere (Perry), and may produce symptoms of food poisoning resembling those of the Salmonella group. The importance of this infection has been recognized in England and in America during recent years as a cause of dysentery and diarrhoa of definite seasonal occurrence, especially in children. The colonies of this bacillus tend to assume a much more crenated outline than do those of the Flexner type, but are usually larger than those of Shiga or Flexner on MacConkey's medium. Cultures of Sh. sonnei are not agglutinated by standard Flexner or Shiga sera. When titrated against a specially prepared Sonne anti-serum, agglutination to full titre occurs. Often, however, when freshly isolated, the bacillary emulsion is inagglutinable, but will abstract the agglutinins from Sonne serum by absorption. On MacConkey's medium, Some colonies frequently show a small central point of acidity on a somewhat opaque background. This bacillus is indol-negative and xylose-negative. It ferments glucose and mannite in twenty-four hours, and lactose and saccharose after some days. Serological varieties and strains are now recognized. Though not so toxic as Sh. shigae, Sonne's bacillus, when injected into rabbits, may produce sudden death.

Dysentery bacilli can usually be isolated from the intestinal canal and the mesenteric glands. The organisms have also been obtained from the blood-stream, gall-bladder and joint-effusions. Selective cultivation media, especially for Flexner and Sonne bacilli, have been introduced to render their isolation easier. The best is Leifson's desoxycholate-citrate medium (Haynes' modification).

Apparently both Shiga and Flexner bacilli are encountered in sporadic cases, and some in epidemics, without a preponderance of any one particular type. Shiga's bacillus is more frequent in the tropics than in temperate zones, is responsible for the most severe clinical forms of the disease, and consequently for virulent epidemics.

Toxins.—The O forms of Sh. shiga contain both exo- and endotoxins. The former is insoluble in dilute trichloracetic acid, whilst the endotoxin can be

precipitated from watery solution by means of alcohol or acetone, after removal of the acid by dialysis, yielding 10 per cent. of dry weight of the organisms. There are said to be two endotoxin fractions which are distinguishable by their nitrogen content and toxicity. Adsorption is effected by aluminium hydroxide. The endotoxin appears to be a large molecule complex of phospholipoid-carbohydrate-polypeptide. The chemical properties of the exotoxin are those of a protein. It is thermolabile and its capacity to combine with antitoxin can be Formolized toxoid can be prepared from measured by its flocculation reaction. it, but not from the endotoxin, though exotoxin can be concentrated by ammonium sulphate fractionation. The properties of different dysentery toxin preparations depend upon origin, strains and methods of preparation (Wagner-Jauregg and Helmert, 1942).

Pathology.—The primary lesions of bacillary dysentery (Shiga and Flexner infections) are confined to the solitary follicles of the large intestine, and result in a sinuous "snail-track" ulceration of the folds of mucous membrane. In very acute cases the process consists of intense hyperæmia of the large intestine. which eventually culminates in necrosis of the mucosa of the entire colon, as well as of the last 2-3 ft. of the ileum. Exceptionally, the whole extent of the mucosa of the small bowel may be involved.

As a general rule, the lesions characteristic of bacillary dysentery are most pronounced in the lower part of the intestinal canal, from the sigmoid flexure to the anus. In the stage of necrosis the large gut is contracted so as to resemble a stiff tube, whilst the mucous membrane is converted into a rigid, olive-green or blackish substance (Plate X, Fig. 3). This colour is thought to be due to the staining of the dead tissue by bile-pigments. Occasionally, the necrosis may have a patchy distribution affecting especially the descending and pelvic portions. There are many signs of profound toxemia.

When the necrotic patches have a more local distribution, irregular ulcers, often communicating with one another by submucous sinuses, form and may involve the entire wall, producing a fenestrated appearance. Inflammatory

changes are found in the mesenteric glands, with macrophage activity.

In mild Flexner, Sonne and Schmitz infections the mucous membrane is red and inflamed, and in places there may be small abrasions or even shallow ulcers. Chronic ulceration of the large gut may occur in bacillary dysentery. The smallest lesions are lenticular, involving the mucous surface. The more advanced lesions are represented by ulceration of limited tracts of mucous

membrane, rarely penetrating beneath the muscularis mucosæ. Ante-mortem perforation may supervene, though rarely. For the differentiation of these lesions from those of amœbic dysentery the reader is referred to Table VIII, p. 487. They should be distinguished from those of tuberculous, typhoid, schistosomal origin, or of ulcerative colitis. In some chronic cases the mucous membrane may be entirely destroyed. The bowel then resembles a piece of

chamois-leather with interlacing fibrotic superficial strands.

Mucous retention cysts, due to the formation of pseudo-adenomata from the bases of Lieberkühn's follicles, may sometimes be found as a sequel of bacillary ulceration, as first described by the Editor. They may be recognized as jelly-like elevations forcing up the mucous surface, scattered throughout the length of the large gut. Dysentery bacilli may be isolated from their contents, and they are found in the large intestine of "carriers" of bacillary dysentery (Fletcher and Jepps) and undoubtedly represent the cause of this condition.

Many cases of chronic bacillary dysentery exhibit no ulceration, but a granular condition of the mucous membrane of the large gut. The lesions are distributed, as a rule, irregularly, usually confined to the lower portion of the large intestine. Considerable infiltration of the walls of the gut is associated with this condition. As in ulcerative colitis, stenosis and shortening of the large intestine, either localized or general, may result. Mixed infection of amœbic and bacillary dysentery may be sometimes met. The spleen shows congestion of pulp and reticuloendothelial activity. The kidneys in Shiga infections may show patchy glomerular congestion and catarrhal changes. In cases of longer duration they are enlarged and the convoluted tubules necrosed, with extensive cloudy swelling. Nephritis is often the cause of death (Dick, 1942). Emboli in liver and spleen frequently occur.

Histopathology.—The submucosa is the seat of numerous hæmorrhages and of round cell-infiltration (Fig. 67). The ganglion cells of Auerbach's plexus are involved in perilymphatic inflammation. The formation of macrophage cells from the capillary endothelium of the vessels may also be observed. Owing to their large size, hyaline appearance, and vacuolated protoplasm, these cells, especially in microscopic sections, are apt to be mistaken for Entamæba histolytica (Plate XI). These cells appear in an early stage in acute ulcers and in the granulation tissue of chronic lesions.

The pathological appearances of Sonne dysentery are not so well known as are those of Shiga and Flexner infections. The changes are, on the whole, similar, but not by any means so severe (Plate X, Fig. 2).

Symptoms.—After a short incubation period, usually of from one to seven days (as ascertained by experiment), the disease commences in a variety of ways, suddenly or insidiously, in all degrees of severity from mild diarrhosa to an acute fulminating attack.

The main clinical symptoms are those of inflammation of the large intestine, viz., griping, tenesmus, frequent passage of loose, scanty, muco-

sanguineous stools, often with dysuria.

The onset may be attended by high or moderate fever, or there may be no rise of temperature. The symptoms may be grafted on to some general disease such as scurvy or malaria, or to some chronic disease of the alimentary canal, as sprue; they may assume acute characters, or they may be subdued from the outset. As a general rule, the closer to the rectum the lesions are placed the more urgent the tenesmus: the nearer the excum the more urgent the griping. General constitutional symptoms due to the absorption of toxins may be evident. Vomiting may occur from the outset, or be absent altogether.

Palpation of the abdomen is difficult during the early stages, owing to the rigidity of the recti muscles. Later, especially in toxic cases, the abdomen may become quite lax, and the spastic sigmoid colon can be sensed as an elastic cord. Implication of other portions of the large intestine can

usually be detected from tenderness on pressure.

Blood changes.—There are few characteristic blood changes. As a rule, there is a polymorphonuclear leucocytosis of 16,000-30,000 at the commencement of the attack, falling to normal or subnormal on the third or fourth day.

Character of the stools.—At first fæcal and diarrheeic, the evacuations may vary enormously in number and character. Their number may be uncountable, with the unfortunate victim "glued to the commode." At first they consist of viscid blood-stained mucus, which bears some resemblance to "red-currant jelly" or "frog's spawn." They are

generally odourless. The characters by which they may be distinguished from amœbic stools are given on p. 502. A few teaspoonsful may be passed. Subsequently they contain less blood and become more purulent. Finally, biliary pigments re-appear and fæcal characters may be re-established.



Fig. 67.—Microscopical section of large intestine in bacillary dysentery, showing necrosis of mucosa, cellular infiltration, and hæmorrhages into submucosa.

In the most acute and fulminating forms the mucus may be mingled with a large amount of altered blood and the evacuations come to resemble "meat washings." When necrosis of the mucosa has taken place the stools may be exceedingly offensive, grey, and contain much altered blood, but no mucus.

On clinical grounds, bacillary dysentery may be classified as follows:

1. Mild or catarrhal bacillary dysentery.—A common history is that for some days the patient had suffered from what was supposed to be an attack

of diarrhea. The stools, at first bilious and watery, perhaps four or five in the twenty-four hours, latterly and by degrees became less copious and more frequent, less fæculent and more mucoid, their passage being attended by some straining and griping.

At the same time the tongue may remain clean, and there may be no accompanying pyrexia. The attack may be over in a week, and the stools may number about twelve in the twenty-four hours. The majority of these mild cases are caused by Flexner, Schmitz, Newcastle or Sonne bacilli.

2. Acute bacillary dysentery.—In others the onset is much more abrupt. Within a few hours dysentery may be in full swing. The stools, at first fæculent, soon consist of little save blood-stained mucus. Very shortly the desire to stool becomes increased, the griping and tenesmus being accompanied, perhaps, by distressing dysuria. Fever, which at the outset may have been smart and preceded by rigor, subsides. The face is anxious

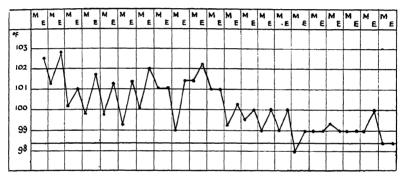


Chart 22.—Bacillary dysentery.

and pinched; the cheeks are high-coloured from a toxic flush. Slight delirium and mental confusion may be added to the clinical picture. Thirst may be considerable, anorexia complete, and the tongue white or yellow-coated. In a week or more the urgency of the symptoms may diminish, and the attack tapers off into a subacute or chronic condition, or it may end as abruptly as it began (Chart 22).

3. Fulminating bacillary dysentery.—These are invariably Shiga infections. The attack generally begins suddenly, it may be in the middle of the night, with chills or smart rigor, vomiting, headache, and a rapid rise of temperature to 100° or even 104° F. Very shortly after the rigor, purging begins, the stools rapidly assuming dysenteric characters. In from two to three days up to a week or longer, peripheral vascular failure sets in with a subnormal temperature, and the patient dies. Sometimes the toxemia may be so virulent that death may take place before dysenteric stools are passed. The tongue is thickly coated, whilst other signs of an acute toxemia are present. The abdomen is sunken and acutely tender. The stools rapidly become liquid, offensive, and greenish or greyish. In the terminal stages neither blood nor mucus may be visible in the almost uncountable evacuations.

A choleraic form, in some respects resembling cholera, has been noted. The onset is acute, with vomiting. Collapse with its attendant phenomena sets in early. The stools are liquid, serous, light-coloured, with blood and mucus in flecks. The temperature is subnormal and death may take place within three days.

- 4. Relapsing bacillary dysentery.—In a proportion of bacillary dysenteries, although the urgency of the initial attack may subside, dysenteric symptoms do not completely disappear. The stools may recover their fæculent character, or may even show some signs of formation, yet they continue to be passed too frequently, often preceded by griping, and containing variable amounts of muco-pus, with or without blood. Cases of this type may be due either to a fresh or to recrudescence of an old infection.
- 5. Chronic bacillary dysentery.—In a large proportion of cases of acute dysentery the fæces do not become absolutely normal for a considerable time after abatement of the more urgent symptoms. On the slightest indiscretion the symptoms re-appear provoking unexpected attacks of diarrhæa. For months, or even years, some patients never pass a perfectly healthy stool, the unformed stools always containing muco-pus or at times blood. There may be a tendency to scybalous stools, or to constipation alternating with diarrhæa.

At the close of the 1914-1918 war a type of chronic bacillary dysentery became quite common. The initial attack may have been so mild as to pass unnoticed, but recurrences take place, with passage of blood and mucus, becoming more frequent and intense as years roll on. Eventually

the stools come to resemble those of chronic ulcerative colitis.

The following varieties may be distinguished:—Those with superficial ulceration from which the causative organism may be isolated by rectal swabs; those without actual ulceration, but with patches of granulation tissue in which cultures are negative; and finally those with generalized mucosal inflammation and deep involvement of the bowel wall.

The course of these cases tends to be progressive, and, unless vigorously treated with sulphaguanidine, they may terminate fatally. Emaciation may be extreme, especially in native races, so that an adult may weigh less than 49 lb. (Fletcher and Jepps.) Considerable anæmia may develop, with cardiac failure and dropsy. Death may ensue from exhaustion, or from some intercurrent disease, such as tuberculosis or malaria. This chronic form was conspicuously absent during the course of the recent world war.

6. Granular rectitis, a granular excoriation of the last three inches of the rectal canal, with the passage of blood and mucus, persists as a not-uncommon sequel, especially in Shiga infections. The general health is good, in spite of it being a most disagreeable complication.

Bacillary dysentery in children.—Infection with dysentery bacilli (Shiga or Flexner) in small children, especially in Europeans, may produce most acute and rapidly fatal symptoms. They may expire in convulsions before the intestinal symptoms have had time to develop. Cases may resemble meningismus, and at their onset, on account of the pyrexia and toxemia, simulate enteric infections.

Post-dysenteric ascites.—Megaw is of the opinion that the ascites which is so common in most hospitals in India is a sequel to bacillary dysentery. When bacillary dysentery remains untreated, or is improperly handled, the dysenteric toxins pass through the intestinal wall and set up an irritative peritonitis which gives place to fibrosis of the peritoneum. The result is ascites, which, according to Snapper, may be associated with liver cirrhosis. Massive serous intraperitoneal effusions, many of which proved fatal, were recorded from the Middle East in 1941–1942.

Symptoms of Sonne dysentery.—In most cases mild attacks of dysenteriform diarrhoea are the rule. The fæces are greenish, or vellowish and offensive, with blood-flecked mucus from which the organism may be cultured. In the more acute attacks the symptoms more closely resemble those of Flexner dysentery, with sudden onset of colic, diarrhea and, later, blood and mucus. Sometimes, however, they are still more acute, with pyrexia and vomiting. They may assume an alarming aspect reminiscent of salmonella infections. Then "tomato soup" stools are passed, followed by rapid prostration. Sonne infections are usually pyrexial at the time of the abrupt onset, but in the milder cases the fever is slight and transient. A feature is associated catarrh of the respiratory tract with diarrhoea. Rhinitis may precede the abdominal symptoms. Acute Sonne infections, in children up to nine years of age, may cause sudden death. Some observers believe that in this instance the symptoms are produced, not so much by the organisms, as by their toxins in contaminated food, which forms a favourable medium for their growth. In mental institutions, especially, Sonne infections are apt to attack inmates.

Cruickshank and Swyer found that, by repeated examination of fæcal specimens and rectal swabs, Sonne's bacillus could be isolated with certainty in most cases, but that the latter method gave a higher proportion of positive results. Sonne's bacillus persists in the intestine in a gradually decreasing proportion of cases after subsidence of the acute manifestations. Thus, the convalescent carrier becomes an important reservoir for the spread of this infection. Three consecutive negative laboratory reports to this effect should be obtained before the patient is released from hospital.

Predisposing causes.—Bacillary dysentery is especially apt to attack those who are in an enfeebled state owing to starvation, unsuitable dietary, physical exhaustion, or exposure, or whose health has been undermined and resistance lowered by some chronic infection such as malaria, tuberculosis, scurvy or enteric. In the feeble-minded, in very young children, in the aged, and in pregnant women, bacillary dysentery is apt to assume a serious toxic aspect. Young children usually show pronounced symptoms of toxæmia, and die in convulsions, or in coma.

Complications.—Dysenteric arthritis, or dysenteric rheumatism was formerly common. Effusions into the cavity and ligaments surrounding the joints, especially the knee and ankle, may take place during the acute stage, or, more generally, during convalescence when the stools are fæculent (Fig. 68). It may be common in some Shiga epidemics, absent in others.

Pyrexia is usually present. The condition may last a considerable time, but usually clears up without leaving any deformities, though, exceptionally, permanent disability with development of osteoarthritis many years later may result. According to Graham, complete recovery usually ensues, even after the arthritis has persisted for six months. Aspirated synovial fluid is sterile, but agglutinates dysentery bacilli (Klein) in a titre considerably higher than that given by blood-serum. This condition



Fig. 68.—Arthritis of hands and knees in bacillary dysentery.

has to be distinguished from fugitive serum-arthritis, such as sometimes occurs subsequent upon injection of anti-dysenteric serum, and also from acute rheumatoid arthritis.

Eye complications.—Acute conjunctivitis and iridocyclitis are now regarded as symptomatic of a dysenteric toxemia. The former is frequently seen in association with arthritis, whilst iritis supervenes in a small percentage of cases. The pupils are irregular in outline, with ring synechiæ. There is also anterior uveitis, with adhesions to the capsule of the lens, formed by a thin exudate occupying the pupillary space, causing photophobia, blepharospasm and marked circumcorneal hyperæmia. The

¹ Shiga's bacilius has been isolated from the fluid in one instance (Elworthy).

aqueous humour has been found to agglutinate Sh. shigæ, though the tears do not contain specific agglutinins. That the eye and joint complications are due to the dysenteric toxin is indicated by experimental work on animals. This shows that the filtrates of Shiga cultures, when injected intravenously, produce iritis and arthritis, as well as local lesions in the cæcum.

Other complications.—Parotitis, unilateral or bilateral, has been often observed. Intussusception of the small intestine has been found in children, and in acute cases may cause death.

During the recent 1939–1945 war the list of complications has been amplified to include intestinal hæmorrhage, perforation with peritonitis, chronic peritonitis with localized, or general, effusions of peritoneal fluid, pneumoperitoneum, portal pyæmia with multiple liver abscesses, thrombosed piles, rectal prolapse, peripheral circulatory failure in toxic cases, renal failure in Shiga infections, pneumonia, and diffuse purpuric rashes. Non-specific urethritis is now also recognised.

Renal failure, which has clinical resemblances to that found in traumatic anuria (crush injury), results from various factors, in which dehydration and toxemia play a part, leading to reduced glomerular filtration and degenerative changes in the tubules. The urine contains granular casts and albumin, so that azotæmia and oliguria ensue, and may end in uræmia.

Sequelæ.—Stenosis of the large intestine may result from acute attacks. Pain and abdominal discomfort may indicate formation of abdominal adhesions which are an occasional sequel. Rarely, megacolon may be produced. Mucous colitis frequently persists for years. Peripheral neuritis of the legs may follow bacillary dysentery. Post-dysenteric tachycardia, or effort syndrome, a condition of irritable heart, may persist long after dysenteric symptoms have disappeared. Achlorhydria, rarely achylia gastrica, may be responsible for digestive troubles which may ensue.

Bacterium coli infections of the genito-urinary tract frequently complicate chronic bacillary dysentery as the result of the specific kidney lesions produced by dysenteric toxins. This possibly explains the frequency of this infection in tropical residents.

Reiter's disease.—The combination of conjunctivitis, arthritis and urethritis has been described as Reiter's disease by Fiessinger in France, Macfie in North Africa, and by Jackson and Wrigley (1946) in soldiers in the recent war. Some authors term it "pseudogonococcal arthritis." The conjunctivitis is purulent or mucopurulent, often bilateral, with photophobia and lacrymation. There may be iritis, scleritis and keratitis. The urethritis is characterized by a purulent discharge which is bacteriologically sterile. Arthritis usually affects the larger joints and is fugitive in character. Skin rashes are common and general lymphadenitis is a frequent accompaniment. The resemblance to chronic bacillary dysentery is undoubtedly great, and there is still considerable hesitation in recognizing it as a separate disease. The virus has been claimed to have been cultivated by Dunham (1947) and has been found capable of producing conjunctivitis in mice. On the other hand Paronen (1948) and Kokko on the Karelian Isthmus in Finland have found the correlation between Reiter's disease and bacillary dysentery to be very close.

Bacillary-dysentery carriers.—The "carrier question" in bacillary dysentery is probably not such a problem as in typhoid, as the former organisms remain confined to the intestines and to the mesenteric glands.

There are many circumstances which render the "carrier state" difficult to detect. Dysentery bacilli, as a rule, are scarce and liable to escape detection in a feecal stool, though with improved methods of isolation by desoxycholate agar, the carrier rate has been assessed about 10 per cent. It is probable that carriers are the starting-point of an epidemic. The majority are "convalescent carriers," a term which implies that the patients have incompletely recovered, continuing to pass blood, mucus and dysentery bacilli in their stools. There is no evidence that the gall-bladder acts as a reservoir, as in typhoid; or that the "carrier state" persists for any great length of time. The organisms continue to live in retention cysts in the intestinal mucosa, in collections of pus from beneath the scars of ulcers or beneath their edges. The maximum period that this carrier state can persist is about three years.

Carriers of Flexner bacilli are much commoner than those of Shiga. Generally, the Flexner carrier is in good health, while the Shiga carrier is adversely affected. Stewart (1944) found carriers of Flexner, Sonne and Schmitz organisms comparatively commonly amongst the native popula-

tion of Algeria.

Sometimes bacillary inflammation or ulceration is localized to the lower rectum (granular rectitis). These patients thus afflicted pass blood and mucus in their stools, though otherwise appearing in good health. The bacillus may be isolated, by means of rectal swabs, as long as a year after the initial attack. Fortunately they are easily cured by sulphaguanidine (see p. 488).

Microscopic examination of the fæces usually affords little assistance in these cases. The chances of isolating the specific bacillus are considerably increased by making cultures direct from the mucosa by rectal swabs, or from scrapings of ulcers obtained through the sigmoidoscope.

Diagnosis.—Difficulty in the diagnosis of bacillary dysentery on clinical grounds is mainly confined to the milder forms. Whenever possible, a confirmatory laboratory diagnosis should be carried out.

The possibility of malaria breaking out with bacillary dysentery should always be borne in mind, and association with the subtertian parasite can

be particularly serious.

A tentative diagnosis may be made from a microscopic examination of the cellular exudate in the stools by a method known as cyto-diagnosis. For this purpose the specimen should be procured from the patient as early as is possible in the disease. The characteristic feature of bacillary stool (Plate XI), is the preponderance of swollen polymorphonuclear leucocytes, with distinctive ring-like nuclei, which constitute over 90 per cent. of the total cell elements in the stool. The examination should be conducted with a $\frac{1}{6}$ -in. lens and a low ocular (\times 2).

Macrophage cells (histocytes).—These, sometimes 20–30 μ in diameter, are derived from the endothelium of the capillary vessels. They may be round, oval, or bilobed. They are hyaline, and contain in their substance

vacuoles, fatty granules, ingested red blood-corpuscles, even, occasionally, leucocytes. They are non-motile, but, owing to their phagocytic activities, are apt to be mistaken for *Entamæba histolytica*.

The differential-cell picture in dysenteric exudates has been distinguished by Alexeieff as a "pyogram." In amoebic dysentery fæces the cellular elements are few and mononucleated; in bacillary dysentery, numerous and polymorphonuclear, with pseudopyknotic nuclei.

It is important that the significance of macrophage cells in bacillary dysentery stools should be emphasized. Willingness to diagnose amoebic dysentery is very pronounced in almost every tropical country. It is important that pathologists should acquaint themselves with the appearance of inflammatory cells in the fæces, as well as with the different stages of *E. histolytica*, before an expert diagnosis is made.

Entamæba coli, and flagellate protozoa (Chilomastix and Trichomonas), may be seen in considerable numbers in a bacillary-dysentery exudate, especially during the convalescent stages. Some difficulty may be experienced in differentiating E. coli from E. histolytica in bacillary-dysentery stools.

Isolation of the dysentery bacillus.—The stool should be collected in a bed-pan, which should contain no disinfectant, and the patient should be warned against passing urine. A portion of freshly-passed blood and mucus should be picked out by a platinum loop, and, if soiled with fæces or urine, should be rinsed in 5 ml. of distilled water or normal saline solution. The earlier in the illness, the easier it is to isolate the dysentery bacillus. It is, as a general rule, difficult when dysentery has lasted five days or longer. Fæces despatched for laboratory examination through the post, or by messenger over long distances, should be emulsified with a double volume of buffered glycerol saline—I part of glycerine to 2 parts of saline, buffered by the addition of 5 per cent. acid sodi phosph., at pH8. The mixture is tinted with phenol red so that any change in acidity can be detected. Dysentery bacilli are very delicate, and are never present in great numbers, even in freshly-passed stools. The mucus, or two loopsful of the suspension, should be spread, in a spiral manner, somewhat thickly, upon a MacConkey agar plate, or, better, on desoxycholate citrate agar, which somewhat inhibits the growth of Bact. coli. The plate should be incubated at 37° C. in an inverted position for eighteen hours, when the small blue transparent colonies may be examined with a watchmaker's lens. As a rule, Shiga colonies are more refractile and of a more regular outline than are those of the Flexner-Boyd group. It is a good plan to hold a piece of dark paper against the back of the plate to render recognition easier.

Identification of the colonies may be carried out as follows: four or more should be picked off with a platinum spud and transplanted on to agar slopes, and, after further incubation, these subcultures should be emulsified and tested in high dilutions against Shiga and Flexner sera in agglutination tubes. The macroscopic method is usually employed, or the test may be performed on a microscope slide, or on an agglutinometer. By means of a capillary pipette, drops of bacillary emulsion are placed together with an equal quantity of specific sera diluted to 1 in 50. The resulting dilution will then be 1 in 100. After oscillation for three minutes, when the reaction is positive, snowflake agglutination occurs.

After these measures have been taken, diagnosis may be confirmed by inoculating subcultures of the organism into the sugars (Table VII, p. 473). Direct culture by the rectal swab method offers obvious advantages and results in a higher proportion of positives.

Isolation of the dysentery bacillus post mortem.—The bacillus can be isolated from the acutely inflamed mucosa by washing the canal free from intestinal contents and scraping off the blood and mucus with a platinum loop, but from necrotic mucosa this is by no means so easy. In this case the surface must be first seared with a hot knife and incised, when material for culture can be obtained with a platinum loop from the bottom of the incision.

Serological diagnosis.—This is of little value as an aid in the early stages of the disease, or in the very acute or rapidly fatal types in which it is so important to arrive at an accurate diagnosis. The sera of some patients, proved to be suffering from bacillary dysentery by isolation of the specific organisms from the stools, may give negative agglutination reactions.

For the diagnosis of Shiga infections in convalescent or chronic cases, positive agglutination of over 1 in 25 should be obtained. In Flexner infections an agglutination of 1 in 100 indicates a positive result. Davies found dysenteric agglutinins were present in dysenteric stools, even when absent from the serum of the patient, especially during the first week of illness. Blood and mucus from the exudate are shaken up with normal saline, filtered and put up for agglutination in the same way as in the serum test.

Serological diagnosis may be of considerable assistance in chronic bacillary dysentery, where high-titre agglutinations are sometimes obtained, especially with emulsions of the pooled Boyd strains of Flexner bacilli. Serological diagnosis of Sonne dysentery by the agglutination test is also somewhat unreliable, and appears to depend, to some extent, on the strain of organism employed as antigen.

Sigmoidoscopic examination.—Sigmoidoscopy reveals pathological changes in the colon and therefore plays an important part in the differential diagnosis of the dysenteries. It is especially useful in chronic cases, and should be employed wherever practicable. For preparation of the patient, the bowel is cleared out by a warm-water enema. If the patient has acute diarrhea, no castor oil should be given. It is advisable to give 10-15 min. of tincture of opium half an hour previously in order to render the rectum less sensitive. The mucous membrane of the rectum is usually replaced by granulation tissue with surrounding hyperæmia, and assumes the appearance resembling the cortex of a granular kidney; at the same time stenosis of the bowel lumen can be detected (Plate XIII). Superficial oval or circular ulcers, up to 1 cm. in diameter, are also seen in this chronic stage, and sometimes pseudopolypoid outgrowths composed of granulation tissue. In the healing stage the mucous membrane is rose-pink and slightly nodular. Widespread superficial scarring at the site of former ulceration is characteristic and it is possible by this feature alone to assume definitely that the patient had suffered from bacillary dysentery. The passage of the instrument is usually attended by pain due to distension of the bowel wall. This is almost diagnostic, as in amœbic ulceration it is usually painless.

Differential diagnosis of the dysenteries will be dealt with on p. 487.

Prognosis depends very much upon individual susceptibility and physical condition. In the jails of India, in fact throughout that country, though bacillary dysentery was widespread, the case-mortality was very low.

TABLE VIII

DIAGNOSIS BETWEEN BACILLARY AND AMCEBIC DYSENTERY

BACILLARY DYSENTERIES

Acute diseases with a tendency to epidemic spread. "Lying down dysentery."

Incubation period short, 7 days or less.

Onset acute.

Pyrexia common.

Course days or weeks.

Complications: Polyarthritis frequent; eye complications.

Death due to-

(a) Exhaustion.

(b) Toxæmia.

(c) Glomerulonephritis.

Signs: Tenderness over whole abdomen, more marked over sigmoid flexure.

Tenesmus very severe.

Pathology: Acute diffuse necrosis of mucous membrane of large intestine, due to dysenteric toxins.

Ulcers: When present, on free edge of transverse folds of mucous membrane and distributed transversely to long axis of gut.

Serpiginous in outline, with ragged undermined edges, often communicating with neighbouring ulcers; bases consist of granulation tissue.

Intervening mucous membrane hyperæmic. Ulcers rarely perforate. No compensatory thickening of bowel-wall.

Stools: Scanty; many in number.
Bright blood-red, gelatinous, viscid
mucus, odourless, resembling redcurrant jelly.

Reaction: Alkaline.

Microscopic picture: Numerous red cells; polymorphonuclears numerous, with clear-cut ring nuclei, Macrophage cells. Few microorganisms visible (Plate XI).

Blood examination: Leucocytosis in the early stages.

AMŒBIC DYSENTERY

A chronic endemic disease. "Walking dysentery."

Incubation period long; at least 20-90 days; may be more.

Onset insidious.

Pyrexia rare, unless complicated.

Course usually prolonged for years.

Complications: Hepatitis, abscess of liver; abscesses rarely in other situations. Pericolic abscess. Amorbic infection of skin.

Death due to-

(a) Exhaustion.

(b) Perforation.

(c) Hæmorrhage.

(d) Liver abscess.

Signs: Local tenderness and thickening, mostly over sigmoid flexure, transverse colon, and cæcum.

Tenesmus not usual.

Pathology: Local lesions confined to the large intestine, due to the characteristic ulcers.

Ulcers: Commence as small abscesses of submucosa in long axis of gut. "Flask-shaped ulcer," or "Bouton en chemise," "sea anemone" ulcers.

Oval, regular, flask-shape in section, involving all coats; bases consist of necrotic black tenacious sloughs ("Dyak-hair" sloughs).

Not uncommonly perforate; compensatory thickening of bowel-wall. Intervening mucous membrane normal.

Stools: Fæces intermingled with blood and mucus, resembling anchovy sauce (sago-grain stool). Offensive, smelling of decomposing blood; generally copious.

Reaction: Acid.

Microscopic picture: Red cells numerous and in clumps, polymorphonuclears damaged, often with extruded nuclei. Macrophage cells scanty. Large numbers of motile bacilli and Entamæba histolytica, usually containing ingested red cells. Charcot-Leyden crystals common (Plate XII).

Blood examination: Usually a moderate leucocytosis.

In many thousands of cases among British troops in the 1914–18 war, it is doubtful whether it at any period rose above 5 per cent. Epidemics in indigenous races have been recorded where the mortality registered over 28 per cent. Among debilitated Solomon Islanders it has been as high as 47 per cent. Prognosis is unfavourable in chronic cases, especially in poverty-stricken, malaria-infected, half-starved natives.

Treatment.—The patient should be placed in bed on the appearance of the first signs, and should on no account be permitted to get up in order to pass his motions. A bed-pan should therefore be employed wherever nursing facilities are available. In the choleraic or fulminating cases in which the passage of stools is incessant, it is advisable to dispense with bed-pans altogether. The patient should then be placed upon a waterproof sheet with a gamgee dysentery pad. For this purpose the attendant, for self-protection, should wear rubber gloves, as the discharges are highly infectious.

The stools should be periodically inspected, for by these, supplemented by the appearance of the tongue and the general condition of the patient, the progress of the case can best be ascertained.

Attention should be paid to the diet, which should be nutritious, easily assimilable, and leaving as little residue as possible. Nothing but water should be given for the first twenty-four hours. The best diet is one consisting of tea, jellies, albumin water, rice water, chicken soup, beef tea, Brand's essence, arrowroot, Horlick's, Bengers, sago puddings—any of which may be given at two-hourly intervals in small quantities (6–10 oz.), slightly warmed, at each feed. Non-residue diet should be instituted when blood and mucus have disappeared from the stools. Treatment should be preceded by a mild purge, the most suitable being sodium or magnesium sulphate. The routine treatment with saline aperients was once almost universal, but is not now employed, especially in dehydrated cases.

Sulphaguanidine (p-amino-N-guanylbenzene sulphonamide) is a guanidine analogue of sulphapyridine. It was first prepared by Buttle and colleagues, though Marshall and others have described its chemical constitution. It exerts a bacteriostatic effect on various bacteria in vivo and vitro. It is moderately soluble in water, insoluble in strong alkali.

High concentration can be obtained in the intestine associated with low concentration in the blood (2–5 mgm. per 100 ml.) and tissues. Urinary excretion is three times as rapid as that of other sulphonamides. Although sulphaguanidine may be excreted as crystals, no renal complications have so far been reported. The drug is undoubtedly less toxic than other sulphonamides. The toxic reactions observed include headache, malaise, purpuric skin rashes, mild pyrexia and anæmia. Agranulocytosis or jaundice have never been observed.

The dosage of sulphaguanidine in acute bacillary dysentery is: initial dose of 0·1 grm. per kilo (or $9\frac{1}{2}$ gr. to the stone (14 lbs.) body weight), a maintenance dose of 0·05 grm. per kilo four-hourly for the period during which the number of stools exceeds five per day, and a further maintenance dose of 0·05 grm. per kilo every eight hours until the stools have been normal in number and consistency for two days. Duration of treatment should not exceed fourteen days. If necessary, the course may be repeated.

In chronic bacillary dysentery larger doses are necessary: 0·1 grm. per kilo every eight hours for the first five days, followed by a dosage of 0·05 grm. for a similar period for another five days. This may be repeated in fourteen days. The total dosage in acute cases varies from 18 to 350 grm.; the average effective dose in acute cases is about 130 grm., usually between 100 and 200 grm. In less acute cases the dose should be 18 grm. in the first twenty-four hours, administered in 6 grm. doses three times daily, and

subsequently 3 grm. three times daily for five days.

The effects may be judged by the alteration in the patient's general condition and in the improvement in the stools which, in most cases, become porridgy and fæcal in forty-eight hours. A diminution in temperature, pain and toxæmia take place within twenty-four hours. The mortality rate, in very extensive series reported upon from the Middle East, is less than 1 per cent. Sulphasuccidine appears to be equally effective, according to Poth and colleagues, especially in children. Sulphapyridine and sulphamezathine in maximal doses are also curative, but are more depressing and more toxic. According to Fairley and Boyd, sulphaguanidine treatment should be combined with preliminary dosage with magnesium or sodium sulphate and, after two hours, with gentle colonic lavage employing one pint of normal saline.

Streptomycin injections have been advocated by Hardy and Hulbert

(1948) and appear to be very effective in refractive cases.

Chloromycetin (chloramphenicol).—McFadzean and Stewart (1952) state that sulphadiazine is more effective than sulphaguanidine or succinyl-sulphathiazole. Ross and colleagues have demonstrated the sensitivity of Shiga bacilli to chloramphenicol in vitro and its efficacy in dysentery in children. Ninety-six cases in Hong Kong from January to December, 1951, were treated with chloramphenicol (average total dose 9-5 grm.—individual doses ranging from 7·75–16 grm.) which checked the dysentery in three days. It was also effective in treatment of sulphadiazine-resistant pathogens.

Chloramphenicol is more efficient than sulphadiazine for the following reasons: (1) resolution, bacteriological and clinical, is more rapid; (2) resistance to chloramphenicol has not been encountered, whereas resistance to sulphadiazine is significant; (3) treatment can be commenced

in the presence of salt and water deficiency.

Other sulphonamides.—According to Ferriman, Mackenzie and Scadding, sulphadiazine is the drug of choice in the milder type of case, in doses of 1 grm. five times daily, and it cuts short long-continued diarrhæa. On account of risk of renal complications, sulphathiazole should be used only in cases without dehydration, but it relieves discomfort rapidly.

Phthalyl sulphathiazole closely resembles sulphasuccidine, but is twice as active and is said to be highly specific in Flexner and Sonne infections. The dose is 0.04 grm. per kg. every four hours for 12 doses, then 0.02 grm. at four-hour intervals until the diarrhœa ceases. Brodie and colleagues (1946) think it the drug of choice in the treatment of Sonne dysentery (type III). The average periods of clinical cure were 8.78 days, but

Sayer and Young have had even better results in this type of dysentery with sulphanilylbenzamide and sulphanilyl-amidobenzene, with which bacteriological clearance was obtained in an average of 1–8 days. The total dosage varied, according to body-weight, from 6–44 grm. over a period of four days, where the weight of children ranged from 14–84 lb.

Sulphatriad (compound sulphonamide).—For lessening the risk of crystalluria a high fluid intake and alkalinization of the urine are recommended. Experimental investigations have shown that by combining sulphathiazole, sulphamerazine and sulphadiazine these risks can be avoided and sulphatriad is a mixture of this composition in tablets of 0.5 grm. each. It may be employed for all acute infections and is especially indicated for bacillary dysentery where the dangers of urinary tract complications are increased. The dosage should be the same as that employed for sulphadiazine. Children, weight for weight, tolerate these sulphonamides three times better than adults. The possibility of blood dycrasias, such as early or late leucopenia, agranulocytosis, acute hæmolytic anæmia and thrombocytopenic purpura must be borne in mind. A curious sequel of intensive sulphonamide therapy, to which Howat (1945) has drawn attention, is steatorrhea, especially in chronic relapsing dysentery. In those treated with sulphaguanidine the relationship of onset of fatty diarrhœa to this treatment is striking and it is now suggested that this drug may be a factor in the production of a conditional deficiency by inhibiting the growth of commensal organisms in the bowel. Both sulphaguanidine and sulphasuccidine, given over prolonged periods, so reduce the bacterial flora of the bowel as to inhibit the synthesis of essential factors, such as aneurin, etc.

Opium.—Either by the injection of morphia or in solution, opium is indicated as a means of promoting sleep and relieving pain, if very severe.

Antidysenteric serum.—Since the introduction of sulphaguanidine the value of antidysenteric serum has been discounted. It is now employed principally in toxic Shiga cases. Refined anti-Shiga serum, prepared by the Pope process of partial peptonization and containing 20,000 International Units per ml., is given intravenously in doses of 5 to 10 ml. and may be repeated daily. The anti-toxic effects appear to be transient. It is best combined with sulphaguanidine therapy. No serum reactions have been observed with this new preparation.

Relief of puin.—During the early stages of an attack the patient may suffer much from griping and tenesmus. These are generally relieved by a hot bath, hot fomentations, or turpentine stupes, three or four of which may be sewn into a piece of flannel and laid on the abdomen. This application has the advantage of being very light, of not wetting the clothes, and of keeping warm for many hours. Tenesmus and dysuria are best relieved by hypodermic morphia; by an enema of a wineglassful of thin starch containing 40 or 50 drops of tincture of opium; or by suppositories of morphia and cocaine. Washing out the lower bowel with a pint of hot water, with or without boric acid, is sometimes effectual in removing for a time, or, at all events, mitigating, the incessant desire to go to stool and to strain. Bismuth carbonate, 2 dr., with tincture of opium, 30 min., and thin starch, 2 oz., is also a good sedative enema.

is first inserted into the cæcum and the fæces are allowed to escape through it, thereby placing the whole of the large intestine at rest. Then an efficient opening is made. The lower bowel may be washed out daily with boric acid solution, and the opening may be closed at some subsequent period, after the large bowel has been permitted to rest for three months or more; complete recovery of the mucous membrane has been observed by sigmoidoscopic examination. A colostomy bag is fitted. The patient may be sent to convalesce and encouraged to consume plenty of fresh eggs, milk and fruit. One-barrelled ileostomy is sometimes preferable and is recommended by some surgeons. The indications here are the same as in ulcerative colitis, but it condemns the patient to a permanent colostomy belt and other disagreeable sequelæ.

Granular rectitis is best treated with suppositories of succinyl sulphathiazole (Cluer, 1947). These suppositories are longer and bigger than those usually supplied. They are composed of succinyl sulphathiazole 3 grm., cocoa butter 7 grm.

The powdered succinyl sulphathiazole is placed in a warm dish and half the quantity of cocoa-butter added. The ingredients are stirred to form a smooth paste before the rest of the cocoa-butter is added. When poured into moulds and set, the finished product is over 2 in. long and § in. in diameter. For this special glass tubes are made. These are lubricated inside with almond oil and corked at one end. A palliative drying paste (Siccolam) is applied to the weeping areas of circumanal skin and in the anal canal (Barclay).

Prophylaxis.—The prophylaxis of bacillary dysentery consists principally in securing a pure water supply and in avoiding unwholesome and contaminated food; also in eliminating flies from latrines and in protecting food against them. In barracks, camps, lunatic asylums, and other public institutions, bacillary dysentery should be regarded as an infectious and readily communicable disease, and therefore patients suffering from mild symptoms, or even looseness of the bowels, should be isolated.

To prevent the spread of bacillary dysentery in closely crowded communities, it is important to recognize, as early as possible, all carriers and mild cases which might otherwise escape recognition. Cunningham and others have pointed out that, in the prevention of the spread of bacillary dysentery in jails, it is essential that the stools of the inmates should be inspected daily. Any inmate found passing blood and mucus, even in small quantities, should be regarded as potentially infectious and as possibly constituting a carrier of the disease.

Chemoprophylaxis.—In the closing stages of the recent war in the Far East sulphaguanidine, in doses of 1 grm. daily, was employed for mass treatment of troops in the field with apparent success.

The treatment of carriers.—The chronic carrier has in the past been difficult to treat effectively, but sulphaguanidine has transformed the situation. It is recommended that this drug should be given in maximal doses for periods of 5-7 days, though it is usually necessary to repeat the course. For the drug to exert its maximum action, the fæces must be kept as fluid as possible by means of sodium or magnesium sulphate. Carriers of Sonne's bacillus appear to be especially difficult to cure (see p. 484).

Prophylactic inoculations.—The Japanese workers, and later Gibson in England, introduced an inoculation by which the toxic effects of the bacillus are neutralized by a potent anti-Shiga serum, resulting in an almost complete absence of reaction. The vaccine and serum (sero-vaccine) are enclosed in twin phials, the bacillary emulsion being contained in one arm, the serum in the other. The first dose was 0.25 ml., containing 500 million Shiga organisms mixed with 0.1 ml. of serum; the second dose, given 10 days later, contained 1,000 million organisms with 0.2 ml. of serum.

The results were distinctly in favour of this method of protection.

Blanc and Caminopetros employed intramuscular injections of living vaccines consisting of 4-6 thousand million dysentery bacilli, and found that they caused slight reactions which resolved three or four days later. They concluded that there is no particular danger in using living vaccines.

Trials have been made with preparations containing dysenteric endo- and exotoxins, and also phenol-extracts of the O antigen of *Shigella shigæ*; this latter excites the appearance of specific agglutinins in the serum after inoculation (Morgan and Schutze).

Sanitation.—For the prevention of bacillary dysentery, and indeed most intestinal infections, the bored-hole latrine appears to offer the best solution for the disposal of rural sewage. With coarse subsoil, contamination from such a latrine may spread in the direction of subsoil water. The bored-hole latrine is easy to instal. There is no smell and the contents lie more than 3 ft. from the ground surface. There is no fly-breeding. After the hole has been refilled the superstructure can easily be moved to another site.

Construction.—The bored-hole latrine is a round hole bored into the earth with a special auger, 16 in. in diameter, and the depth depends on the subsoil water level—a minimum of 3 ft. during the dry season. A hole 6 in. deep and 16 in. in diameter is first dug and the auger is placed in this hole and rotated clockwise. If the soil is very loose the hole can be protected by putting in a bamboo lining. A squatting plate is of reinforced concrete 3 ft. by $2\frac{1}{2}$ ft., made in the following proportions: cement 1 part, sand 2 parts, stone and brick chips 4 parts. The thickness of the plate is 2 in. and sloped $1\frac{1}{2}$ in. from edge to centre. The plate is reinforced with $\frac{1}{2}$ -in. diameter rods.

II. AMŒBIC DYSENTERY AND AMŒBIASIS

Definition.—Amœbiasis denotes infection with the protozoan, *Entamæba histolytica*. When confined to the intestinal canal it produces amæbic dysentery, or primary intestinal amæbiasis. This is insidious in its onset, chronic in its course, and with a marked tendency to relapse. When metatastic lesions are produced in the liver and elsewhere they should be known as secondary, or hepatic amæbiasis.

Geographical distribution.—Amœbiasis occurs to a greater or lesser degree throughout the tropics and subtropics. During recent years sporadic indigenous cases have been found in Northern Europe (Russia, Norway and Germany) and even in Great Britain. Specially prevalent in India, Indo-China, China, and the Philippines, it is common throughout North and Central Africa, widespread in the Southern United States, South America, and the West Indies.

Epidemiology and endemiology.—A disease of insanitation, not necessarily requiring tropical or subtropical conditions for its propagation, amæbiasis arises sporadically without seasonal prevalence, but does not usually occur in epidemic form in the same manner as the bacillary dysenteries. Wenyon and O'Connor have shown that the cysts of E. histolytica can be demonstrated in the fæces of house flies sixteen hours after ingestion, and that flies play a part in dissemination. Roberts (1947) has demonstrated E. histolytica cysts also in the fly's vomit. The evidence is that they are not derived from the crop, but represent those which become wedged in the pseudo-tracheæ and are later flushed out by fluid from the crop or from the salivary glands. There is also much evidence that contaminated water and even fresh vegetables, such as lettuce, may constitute sources of infection.

It has now been shown that wild rats, especially R. norvegicus, are frequently infected with E. histolytica and may aid in its dissemination (Neal, 1948). This has recently been confirmed (1951). E. muris, a species indigenous to the rat, closely resembles E. histolytica.

Reports of the outbreak in Chicago in the summer and autumn of 1933 gave the total number of cases as 1,409, in that city or traced to others in the United States, with over 40 deaths. The source was traced to two hotels, where the majority of those infected were servants or guests. All carriers of *E. histolytica* were removed from employment, but in spite of these measures, cases continued to develop amongst employees of one hotel, where the "carrier" rate was found to be as high as 47.4 per cent. Further investigations revealed serious contamination of the water supply from defective drainage so that drinking water formed the main channel of infection. Morton and associates (1952) have recorded an outbreak of acute amœbic dysentery in an R.A.F. camp in England as the result of gross fæcal contamination of a water bore-hole. In a population of 1,042 at risk, 141 suffered from acute gastro-enteritis, 6 developed acute amœbic dysentery and 11 active amœbiasis of less severity. The majority had never been overseas. Twenty-six symptomless cyst-passers were found.

Amoebic dysentery is frequently a house or family infection as shown in the Liverpool outbreak reported by Adams and Seaton (1949).

Intestinal amœbiasis is a disease of adult life as a rule. It is rare in European children under five years of age, but among Egyptians of the poorer class in Cairo, Perry and Bensted found that 13 per cent. of clinical dysentery was due to *E. histolytica*. Biggam diagnosed acute amœbic dysentery with liver abscess in an infant three months old, and Williams found it in a negro infant of fifteen months on the Gold Coast. As the disease has a long incubation period and is acquired from contaminated water and vegetables, it is unlikely to occur among carefully nurtured children, in whom the bacillary form is more frequent.

Intestinal amœbiasis may produce active symptoms for many years. The Editor has treated infections which have persisted from thirty to forty, and in one for fifty-four, years without seriously undermining health, so tolerant are the tissues to E. histolytica. There appears also to be a difference in incidence of intestinal amœbiasis in the sexes. Males, European and entire, are more apt to contract the infection. Gharpure and Saldanha (1930) reported that in a series of over 400 post-mortem examinations the number of male cases was quite disproportional to the total. Of amœbic dysentery and liver abscess,

90.6 and 93.8 per cent. respectively occurred in males; 9.4 and 6.2 per cent. in females. Below ten years of age the incidence of amœbic lesions was 0.9 per cent. and of liver abscess nil. The highest peak is reached in the decennial periods 20-40, with a proportion of about 30 per cent. of amœbic dysentery and 38 per cent. of liver abscess to the total number of autopsies.

In Armenia, Zaturjan showed that ameebiasis in children usually runs a much more benign course than in adults and rarely shows any serious complications.

Ætiology.—The discovery of amæbæ in dysentery stools was made by Lösch in 1875. Originally regarded as a single organism—Amæba coli—it is now recognized, mainly as a result of the work of Schaudinn, Hartmann, Wenyon, and Dobell, that several distinct species occur in the intestinal canal of man, one of which, Entamæba histolytica, is pathogenic, while others—Entamæba coli, Endolimax nana, Iodamæba bütschlii and Dientamæba fragilis—are harmless species. E. histolytica was originally cultured on egg-medium by Boeck and Drbohlav in 1925, but during the last few years it has been grown on a variety of serum-media. E. histolytica can be grown in microtubes in symbiosis with Trypanosoma cruzi. For successful culture the presence of bacteria is necessary, although excystation can take place in the absence of bacteria when complex organic substances are added to the medium.

Detection of Entamæba histolytica in stools.—When present in stools, entamæbæ are generally easy to find. It is necessary to pick out a small fragment of stool shortly after it is passed, and to lay it on the slide and compress it under the cover-glass to form a fairly transparent film. Active entamæbæ tend to occur in clumps or masses and are not evenly distributed throughout the stool: they may be present in one evacuation, but not in the next. Care should be taken that the receptacle in which the stool is collected is free from all traces of antiseptic. These amœbæ live in the fæces for a few hours after being passed and are distorted in the presence of urine. The dysentery amœba is a clear, faintly greenish-tinted, transparent body, as a general rule, some three to five times the diameter of a red blood-corpuscle. By staining the background with dilute eosin the refractile appearance of E. histolytica becomes more apparent. In its vegetative or tissue-invading phase it is recognizable by its active movements, as well as by the presence of extraneous material, such as red blood-corpuscles, which it ingests. The nucleus may sometimes be eccentric. The habit of ingesting red blood-corpuscles and body-tissue cells is one of the points of distinction between E. histolytica and non-pathogenic E. coli.

In fresh and in stained preparations the ameeba is seen to be made up of two zones—a granular endoplasm surrounded by a clear protoplasmic ectoplasm. The nucleus shows a characteristic uniform structure, if the specimen is fresh and fixed while alive; aberrant forms with fragmented karyosomes, etc., are due

to degenerative changes (see p. 919).

These amede flow, rather than move, across the slide, and in the living state do not always exhibit conspicuous differentiation between ectoplasm and endoplasm as described. They quickly die and degenerate outside the body. At lower temperatures they remain stationary, but when the slide is warmed, they eject from time to time hyaline "blade-like" pseudopodia (Fig. 69). Degenerating entamede often contain vacuoles, but these are not normally present. When conditions become adverse, they encyst, first passing through a precystic stage.

Cysts.—Cysts vary much in size. They contain highly refractile masses of chromatin, or chromatoid bodies, which may assume the form of blocks with

¹ For the staining of amœbœ in liquid preparations, Schaudinn's method is employed. The details of amœbœ are distorted if attempts are made to dry the specimen as in a blood-film.

rounded ends, and also glycogen-containing vacuoles. When first formed, the cyst contains one nucleus, which measures about one-third of its diameter. This divides by binary fission, so that finally, in the more mature individuals, four small nuclei, each measuring one-sixth of the diameter of the cyst, are produced. In general characters the nucleus of the cyst resembles that of the vegetative stage.

Cysts of E. histolytica can survive outside the body of man for about ten days, if kept moist and cool. Desiccation kills them immediately, though they survive

much longer at lower than at higher temperatures.

Westphal has recorded a significant experiment where an apparently harmless E. histolytica infection was acquired by the ingestion of cysts. Some months later cultures of bacteria isolated from the fæces of acute amæbic dysentery were ingested and a similar dose was given to a control. Both the "carrier" of E. histolytica and the control suffered from diarrhæa, but on the twenty-third



Fig. 69. Camera lucida drawings showing protrusion of pseudopodia by Entamæba histolytica. (P.H.M.-B. del.)

day, the former developed clinical amœbic dysentery. It was finally determined that super-infection with Flexner bacilli excited the clinical manifestations of amœbic dysentery. Some workers therefore believe that symbiotic bacilli aid, or in some way instigate, attacks of acute amœbic dysentery. This view has been to a great extent confirmed by Hoare (1949), who has shown that in the great majority of cases the amœbi is coprozoic and feeds on bacteria and fæcal debris. In amœbic dysentery, however, it feeds on erythrocytes. In experimental infections of rats it shows every gradation from a commensal life to true parasitism. In monkeys E. histolytica usually produces a symptomless infection and feeds on micro-organisms, whilst in cultures it may ingest starch granules. In addition to this method of nutrition E. histolytica takes up food saprozoically by absorption of fluid through the surface of its body.

Summary of life-history of Entanacha histolytica.—The active vegetative entanachæ live on the tissues of the gut-wall, where they ingest blood-corpuscles and multiply by mitosis. In primary amæbic lesions they make their way into the follicles of Lieberkühn, where they multiply and, partly by pressure, partly by cytolysins, dissolve the interglandular tissues, producing small amæbic abscesses in the submucosa which subsequently burst and become ulcers. A number of amæbæ then enter the lumen of the bowel, encyst, and pass out with the fæces. The precystic individuals, which are free from protoplasmic inclusions, congregate on the surface of the mucosa. They are smaller than the vegetative forms which continue to multiply in the tissues. Typical cysts, which are smaller than precystic forms, are quadrinucleate when fully mature. When swallowed by another host they pass into the small intestine, where they hatch into amæbulæ which again attack and invade the tissues. (See Appendix, p. 920.)

¹J. A. Beyniers has failed to produce amoebic infection in rats under conditions of complete sterility (1953).

This summary epitomizes the generally accepted account of the lifehistory of E. histolytica, but there are some observers, notably Reichenow and Hoare, who consider that it is normally an inhabitant of the lumen of the intestinal tract and not a tissue-invader (in the condition known as "cyst carrier"), but that, under certain conditions, the amœbæ may invade the intestinal wall and thereby give rise to clinical amœbic dysentery. They think that the normal is the minuta form, which lives in the intestinal lumen, where it reproduces by binary fission and produces four-nucleated cysts.

Most clinicians consider that E. histolytica is an obligatory parasite, but it does live commensably in vitro in cultures and can exist commensably in vivo in monkeys. Symptomless human carriers of the infection discharge amœbæ containing bacteria, but no red cells, which indicates a commensal habit. Sigmoidoscopic examinations of "carriers" reveal no lesions in the gut wall and, furthermore, at post mortem the bowel is unscathed. Symptomless carriers may discharge 350,000 non-hæmatogenous amœbæ per grm. of fæces (or 35 million parasites daily) and it is unthinkable that such numbers could infest the intestinal wall without producing any symptoms. Furthermore, after purgation, which causes the discharge of numerous amœbæ, the number of cysts in the stools is lessened suggesting that the parasites have been swept from the lumen of the gut. The case for a commensal phase is contained in the life history of E. histolytica. At least 50 per cent. of symptomless carriers harbour small cysts (under 10 μ in diameter) which do not produce dysentery in cats, will not affect rats and are generally agreed to be harmless to man.

A characteristic feature of amedic infection of the intestine is the periodic variation in intensity, which may be connected with resistance on the part of the tissues of the host, or possibly constitutes a feature

in the developmental cycle of the parasite.

Occasionally, however, vegetative amœbæ migrate from their site in the bowel-wall and, as tissue-invading forms, enter the venous system and are transported to the liver, exceptionally to the spleen, brain or lung; but by so doing they become unable to complete the cycle of development as observed in the intestine, for pre-cystic individuals and cysts are never produced in these situations. Amœbic infection of the skin has been seen quite often (see p. 535).

E. histolytica passers. —The healthy passer (or excretor) of E. histolytica is an individual who has not suffered, and is not suffering, from dysenteric symptoms, but passes histolytica cysts, though otherwise in good health. Such cyst-passers may, or may not, have active entancebæ in the tissues of the bowel.

The cyst-passers may be divided into two classes—(1) contacts who have never suffered from clinical amoebic dysentery, and (2) convalescents who have recovered from an attack. It is known that, for every abnormal person who is suffering from amoebic dysentery with passage of vegetative forms which are non-infective to other individuals, there are large numbers of healthy persons who continue to pass E. histolytica cysts, thus

 $^{^1}$ "Cyst-passer" is here used in the place of "carrier," a term which is not strictly applicable to E, histolytica,

constituting a perennial source of infection. It is thought that in the first case the parasite lives in the fæces, or is commensal, in the second it continues to persist in the tissues of the host (the action of diodoquin on the parasite may afford the correct interpretation (see p. 513)). We know from post-mortem findings in the Philippines, New Orleans and elsewhere that ulceration can occur without producing signs or symptoms, and it is well known that liver abscess may also eventuate under those conditions.

In Faust's opinion the conception of amœbic invasion of the human bowel should include milder types of tissue damage. In a series of accidental deaths in New Orleans thirteen cases of *E. histolytica* infections were disclosed, of which seven showed amœbic lesions. There were three types:—(1) initial pinpoint ulceration, (2) shallow crater-like lesions, (3) extensive very shallow denudation of the mucosa. None of these destructive processes extend beneath the muscularis mucosæ.

The lesions of the mucosa may be microscopic. Cytolysis and necrosis of the epithelium is followed in the majority of instances by rapid regeneration, so that probably only a small percentage develop clinical evidences of amœbic dysentery. The experiments of Walker and Sellards showed that, out of 20 men fed with *E. histolytica*, 18 became parasitized, but only 4 developed dysenteric symptoms, though the remainder continued to pass cysts in their stools.

By intrarectal and intracecal injection of feeces containing cysts into cats and puppies, ulceration of the bowel-wall and hepatic abscesses have been produced; but, although the feeces may be swarming with active vegetative forms, no cyst-formation has ever been observed in these animals. Similar lesions have been produced in kittens by intrarectal injection of cultures of *E. histolytica*.

Intracæcal infection of young white rats with cultures of *E. histolytica* has proved in recent years a valuable method of studying this parasite and the action of specific drugs upon it (W. R. Jones, 1946; L. G. Goodwin, 1947). By these means they have shown that strains from different sources vary in their infectivity and that pathogenicity does not depend upon the number of amebæ injected, or upon the severity of the human infections from which they were derived.

Infection in carriers of *E. histolytica* is remarkably persistent and, in all probability, unless cured by anti-amcebic treatment, they may continue to pass cysts for the remainder of their lives.

Craig and other American authorities believe that everyone who harbours *E. histolytica* cysts is a candidate for some more serious complication and that therefore every "carrier" should receive adequate treatment. As there are many authentic instances where the infection has been observed to die out in absence of specific treatment, this is probably an overstatement.

Incidence of cyst-passers or carriers.—Among British soldiers after a year's service in Egypt, Wenyon and O'Connor found that there was no marked difference between carriers who had previously suffered from dysentery and those who had not (the percentages being 6.5 as against 4.5 per cent.). The carrier rate among native Egyptians, as might be surmised, was considerably higher, 13.5 per cent. The most surprising outcome of the systematic examination of fæces by protozoologists during the 1914–1918 war was the almost universal presence of the histolytica carrier. Yorke, Matthews and Malins Smith found a considerable percentage of carriers among lunatics, army recruits, and the personnel of the

navy in England. The two former recorded 5 per cent., the latter 19 per cent.; Kuenen found a considerable number of indigenous infections in Holland, and Brug estimated the carrier-rate as 12·7 per cent. in that country. In the United States amongst schoolchildren it may be as high as 10·8 per cent., but in adults Andrews and Paulson gave a much lower figure, 0·2 per cent. In New York City it is 1·1 per cent. among city dwellers, 5·4 per cent. among foodhandlers, and in Philadelphia 5·2 per cent. for the general population. Craig has estimated that 10 per cent. of the total inhabitants of the United States are infected with amediasis. The exact significance of these figures is difficult to determine. It certainly does not mean that this comparatively large number is suffering from gross ulceration of the bowel, for indigenous amedic dysentery is very uncommon in England. Even among the insane, with a relatively high cyst-passer rate, "clinical amedic dysentery" is rare. Belios and Cooper (1953) have now proved that in mentally deficient children in Hertfordshire the incidence of E. histolytica infection may be 40 per cent.

A single microscopic examination probably detects one third of the cases so that the true percentage of "carriers" in a normal population is about 10 per cent. for *E. histolytica*, 36–54 per cent. for *E. coli* and 13 per cent. for *Endolimax nana*. Infection is probably acquired at an early age. Evidence suggests that infection of the same order occurs in France, Holland, Germany and other European countries, yet amoebic lesions of the intestine and liver are rarely found.

Pathology.—The earliest lesions of amœbic dysentery are minute yellow hemispherical elevations of the mucosa, which mark the site of a deeper-lying zone of necrosis. By growth in size and localized necrosis they form flask-shaped ulcers, the bases of which lie in the submucosa. These ulcers are scattered throughout the large intestine, rarely extending above the ileo-cæcal valve. The appendix may be involved, and Musgrave, in 1910, reported three cases of fatal peritonitis due to this; since then a few other cases have been investigated in which entamæbæ were demonstrated in microscopic sections. Amæbic ulceration of the ileum has been described by Biggam. These were acute and rapidly fatal cases, and in neither instance were amæbæ demonstrated in the stools, but in preparations from the lesions.

The ulcers may not be larger than a pin's head or may measure an inch or more in diameter, and, as the disease progresses, may become even larger. Then the margins are rolled, the edges undermined, and the base is formed by fibres of the muscular coat (sea-anemone ulcers). The ulcers are capped by dense yellow, green, or even black sloughs (Dyakhair sloughs), which may project into the lumen of the bowel. The lesions usually originate in the cœcum, are scattered throughout the transverse, sigmoid colon and rectal canal. Uusually the intervening mucous membrane remains healthy. Amœbic lesions commonly extend throughout the large intestine as far down as the internal anal sphincter.

In 186 cases examined post mortem by Clark in 1924, lesions were scattered throughout the colon in 61 per cent. affecting, in order of frequency, excum, ascending colon, iliac colon, sigmoid, rectum and hepatic flexure. At the sites where intestinal stasis is greatest there is a tendency for amœbæ to invade the bowel wall.

In chronic amcebiasis there is inflammation and hypertrophy of the bowel-wall. Sometimes sacculation and stenosis of the large intestine may be produced by cicatrization (Plate X, Fig. 1).

Sellards and Leiva demonstrated in experimental animals that when the excum is exposed and infective material is introduced into the lumen, infection takes place with surprising regularity, but that, whether it is introduced directly into the excum or via the rectum, initial lesions occur in the extreme lower part of the bowel. Stasis in the large intestine affords the organisms a foothold, and is a factor in determining the location of the initial lesion. Wagner and Beiling, whose conclusions are almost identical, found that the amœbæ at these focal points enter the tissues in one of three ways, passing directly into connective tissue, crypts, or lymph-channels, where they migrate to the lymph-follicles and the submucosa. The intestinal mucosa responds to invasion by secreting mucus, which, when mingled with blood, forms an excellent medium for the development of amœbæ on the bowel surface. The balance between host and parasite is delicate.

Thrombosis of the blood-vessels, in which entamcebæ are often found, occurs at the bases of the ulcers, and, by erosion, an arteriole may be opened, and severe or fatal hæmorrhage may result. Perforation by ulcers, even massive gangrene, especially of the cæcum, may also occur, and lead to fatal peritonitis. The ragged ulcerated mucosa becomes

readily infected with pyogenic organisms.

In the healing gut, cicatricial pigmented scars mark the sites of former ulcers. Adhesions may form between proximal coils of intestine which become matted together or adherent to the liver and spleen. Pericolic abscesses may also sometimes form.

In chronic cases, polypoid or gangrenous tags project into the lumen of the gut. The intestinal contents may be composed of dark, almost black hæmorrhagic fæcal matter with characteristic penetrating odour. Carcinoma may originate at the site of healed amæbic lesions.

The cadaver shows no signs of toxic absorption, such as occurs in the bacillary dysenteries. Apart from wasting, the other viscera exhibit

few, if any, changes.

In the last years considerable attention has been paid to the amœboma, or amœbic granuloma, which results from repeated amœbic invasion of the colon with superadded pyogenic infection, producing progressive inflammatory lesions. This process spreads through the bowel wall into the pericolic and perirectal fat, infiltrating the surrounding structures. The resulting tumour consists of fibrous tissue, granulations and varying degrees of ulceration. Typical amœbic ulcers may be present on the surface of the tumour, or no naked-eye presence of amœbiasis may be forthcoming. The usual sites are the rectum, rectosigmoidal junction and cœcum. Differentiation from carcinoma may be difficult.

Histology.—The amœbæ work their way down the crypts of Lieberkühn, multiply, and, by secretion of cytolysins, disintegrate the tissues of the submucosa and produce gelatinous necrosis, with little surrounding tissue reaction and round cell infitration (Fig. 70). In more advanced lesions the entamœbæ may be seen between the muscular fibres and within the peritoneal veins, whence they may be swept as emboli into the portal vein, lodge in the liver, and so become the starting-point of amœbic hepatitis or liver abscess.

The superficial layers of the slough of an amobic ulcer become secondarily invaded by bacteria, though the adjacent mucous membrane remains healthy and shows few microscopic changes. The precystic forms of *E. histolytica* are

found in the intestinal mucus and on the surface of the bowel.



Fig. 70.—Section through base of amoebic ulcer, showing E. histolytica in the tissues. (C. M. Wenyon.)

Experimentally-produced amœbic dysentery in kittens differs essentially from the disease seen in man. When introduced into the rectum of the cat, entamœbæ produce acute inflammation within two to three days. The lesions differ in their generalized and acute character from those observed in man. Death takes place from secondary terminal bacterial invasion. Cysts are never found, and chronic ulceration does not occur.

Symptoms.—The incubation period of amœbic dysentery, from the time of introduction of the cysts into the intestinal canal until the development of symptoms, may be of considerable length. In the Chicago outbreak of 1938 it ranged from seven up to seventy-seven days, symptoms appearing occasionally within one week though, in a few instances, not for three or four months. The fact that amœbic cysts are found in the fæces of individuals who may never have had "dysentery" in the ordinary accepted sense, suggests that the development of clinical symptoms may possibly depend upon some secondary bacterial infection.

The great majority of cases of amcebic dysentery run a chronic course, with frequent intermissions and relapses. This latency is one of the most striking and characteristic features. The *onset* is generally insidious, so that the patient may complain more of diarrhea than of dysenteric

symptoms. Perforation of the bowel, leading to fatal peritonitis, has been known to occur in patients who, judged by clinical appearances, were not suffering from dysentery. In mild cases the patient generally complains

of suddenly developing amæbic diarrhæa.

The symptoms, subjective and objective, may closely resemble those of bacillary dysentery; but, as a rule, abdominal tenderness is much less acute, and may be restricted to the cæcum, thus simulating appendicitis. or to the transverse colon, where it may mimic gastric ulcer; more frequently, however, it is limited to the sigmoid flexure. Should ulceration occur in the rectum, tenesmus and straining may ensue. The individual stools are larger than those of bacillary dysentery. They may not exceed three or four in the twenty-four hours, but are seldom more than twelve. As a rule, they contain much dark and altered blood, which exudes a penetrating, disagreeable odour. In consistence and appearance they resemble anchovy sauce. Often, blood-streaked mucus is intermingled with liquid fæces. Melæna may occur occasionally. The motions may sometimes be formed, and streaked with blood and mucus. Gangrenous sloughs may be voided. Unless the case is complicated by hepatitis, when the liver is painful and enlarged, there are seldom any toxic manifestations. Acute cases of amœbic dysentery with high fever and urgent painful and severe clinical manifestations are rare. In the Chicago epidemic acute cases of unusual severity, with pyrexia and other toxic manifestations (amœbic fever), were noted.

The patient, as a rule, becomes emaciated, but some remain in remarkably good condition, although suffering from repeated relapses. Some there are who even become grossly fat. Sometimes the skin is myxenoid and the complexion assumes a subicteric tinge. The tongue is moist and coated. Vomiting may rarely occur. Generally there is a complete anorexia. Dysuria is not noted as in bacillary dysentery, and tenesmus is rare. The liver is sometimes enlarged, even in the absence of hepatitis.

In uncomplicated amœbic dysentery, there is usually no pyrexia, but cases with intermittent fever are occasionally met and with high continued fever (amœbic fever), in absence of any ascertainable complications, and these may be recognized by amenability to emetine treatment by the discovery of amœbæ or cysts in the fæces, or by recognition of amœbic ulcers by sigmoidoscopy. In amœbic dysentery there is usually a moderate leucocytosis (10,000–12,000 with low proportion of polymorphonuclears—

about 70 per cent.).

There still remain a number of obscure conditions of which some mention must be made. It is probably true, so variable are the symptoms of amebiasis, that almost any intestinal disease may be simulated. Intestinal amebiasis is not invariably associated with dysentery or diarrhea. It may occasionally be marked by constipation, by lower abdominal pains or disturbances, very often by neurasthenia, bodily and mental lassitude, furred tongue, and disordered digestion, popularly described as an "uncomfortable belly," or "growling abdomen." Acute upper abdominal pain, with vomiting, is not suggestive of amebiasis. Pathological changes in the bowel may sometimes lead to sacculation or even dilatation of the colon. Very often the execum is distended with gas and the source of

much discomfort. In chronic cases, diffuse infiltration of the sigmoid colon, less commonly of the cœcum, can be detected by abdominal palpation.

In the course of prolonged chronic amœbiasis, myxenoid cachexia may ensue, suggesting intestinal toxæmia. These patients have muddy complexions resembling in outward appearances some cases of diverticulitis.

Often, without treatment, symptoms may subside, and the patient may be apparently cured. but will relapse after an interval of weeks, months, or even seven years or longer. More often he continues to pass loose, semi-formed stools. Attacks of diarrhea alternate with constipation. After any physical exhaustion, chill, alcoholic or dietetic indiscretion, a fresh exacerbation may supervene. On account of these variable symptoms, the infinite variety of abdominal pain, and the occasional melænic stools, it is clear that ameebic dysentery has to be differentiated from duodenal ulcer, gall-bladder disease, diverticulitis, pancreatitis and neoplasm.

Anæbic typhlitis.—Amœbiasis of the cæcum may be present without involvement of any other portion of the large bowel. This gives rise to local pain and deep tenderness. Differentiation from appendicitis may be difficult. As a rule, the local signs in the right iliac fossa predominate

over the generalized signs of toxæmia, as in appendicitis.

Amæbic granuloma or amæboma.—The discovery of a sausage-shaped abdominal tumour in a subject of amæbic infection suggests this possibility. Such a tumour may be present in the cæcum, transverse colon, sigmoid or rectum. It may even be the cause of chronic intussusception, especially when situated at the apex of the cæcum (Ogilvie). It is usually hard and indurated, but tends to vary in size from day to day. Differentiation from carcinoma or tuberculoma may prove difficult when E. histolytica

cysts may be absent from the fæces.

Hepatitis.—Acute amœbic hepatitis may supervene at any time during the course of amœbic infection, while the symptoms are acute, or during a remission. The patient usually experiences great pain over the hepatic area, together with signs of toxæmia and pyrexia. His attitude is characteristic: he inclines to the right trying to protect his liver and carrying it in his hands, so to speak. The liver itself is enlarged; it may project below the costal margin to the level of the iliac crests, and then be extremely tender. Pain referred to the right shoulder, due to stretching of the diaphragm, is also frequent. Usually there is a leucocytosis of twenty to thirty thousand with low proportion of polymorphonuclears. A chronic form of amœbic hepatitis without pyrexia or leucocytosis is also recognized.

Hepatitis may subside without any active treatment. There is some evidence that in these cases the amœbæ are distributed throughout the liver, with embolic spread, suggesting a portal distribution. Fortunately in this situation it is particularly amenable to emetine treatment and

chloroquine (see p. 531).

Complications.—Death may result from exhaustion, intestinal hæmorrhage, perforation, or liver abscess.

The most frequent complication of amobic dysentery is liver abscess.

Perforation of the bowel may be sudden, or be preceded by intense local pain, which, when restricted to the right iliac fossa, may be mistaken for appendicitis. According to Howe this is a rare event, but is a very serious one. The bowel is usually so friable that at operation the sutures fail to hold. In subacute perforation pericolic abscess may be produced, especially in the descending or sigmoid colon. Intestinal obstruction from an americ granuloma (american) has been recorded. When such a growth forms in the cæcum it may resemble hypertrophic tuberculosis or malignant disease.

Amæbiasis may be superimposed upon bacillary dysentery, or vice versa. In Egypt, intestinal amæbiasis is often found associated with Schistosoma mansoni. Visceroptosis, distension or sacculation of the bowel, leading to intestinal stasis, may constitute distressing results of amæbic dysentery, but stricture of the rectum does not commonly ensue. Appendicitis due to amæbic ulceration is not uncommon. Snapper has recorded a psoas abscess as the result of perforation of an amæbic ulcer

of the cæcum.

Sequelæ.—Many sequelæ of intestinal amœbiasis have been described often on insufficient evidence, and it is very difficult to prove direct association of different obscure clinical states with a past infection with E. histolytica. The Editor believes that certain intestinal conditions occur frequently as the aftermath of amœbiasis; such are appendicitis (not necessarily caused by amœbic ulceration), and mucous colitis. Chronic amœbiasis, besides producing chronic ill-health, very often contributes to introspection and neurasthenia.

Diagnosis.—It is safe to regard acutely developing tropical diarrhea either as bacillary or amoebic dysentery, though clinical distinctions in the less acute manifestations are often unreliable. Assistance in diagnosis may be obtained from the more rapid onset, the febrile condition, and the rapid pulse in the bacillary disease. As a rule, the number of stools in bacillary dysentery is greater and their individual size less. The character of the stools should also be taken into account. Usually they are more offensive and contain more dark blood in amoebic dysentery. Occasionally, however, they may be tarry, suggesting duodenal ulceration.

Laboratory diagnosis should always be resorted to, having regard to the experience of the observer and his ability to determine whether any ameba-like body discovered in the fæces is in fact E. histolytica, E. coli, or some large tissue cell, such as a macrophage (Plate XI). With practice this becomes comparatively easy. Entamcebæ may be absent in some portions of a stool; numerous in others. Several preparations must be searched, at first with the \frac{2}{3}-in. lens, subsequently with the \frac{1}{6}-in. Whenever possible, a portion of blood-stained mucus must be picked out for examination. The organisms may be difficult, or almost impossible, to detect in a specimen containing too much blood, and it is important that the specimen should be as fresh as possible. The discovery of an active amæba containing ingested red blood-corpuscles is generally sufficient to establish the identity of E. histolytica. In the more chronic and latent forms of the disease the characteristic cysts must be sought.



MICROSCOPIC APPEARANCE OF CELLULAR EXUDATE IN ACUTE BACILLARY DYSENTERY (Shiga infection)

Fresh preparation. Shows macrophage cells with ingested red blood-corpuscles, intestinal epithelium and polymorphonuclear leucocytes.

(P. Manson-Bahr)



MICROSCOPIC APPEARANCE OF EXUDATE IN AMŒBIC DYSENTERY

Fresh preparation. Shows active $Entamaba\ histolytica$, some with ingested red blood-corpuscles: acicular Charcot-Leyden crystals and disintegrated intestinal epithelium.

 $(P.\ Manson-Bahr)$

PLATE XII

It has often been claimed that daily purgation with salts promotes the discharge of amœbic cysts, but this is by no means certain. Concentration methods for the detection of cysts are most useful and cultural methods less satisfactory. Entamœbæ and their cysts can at first be recognized under a low-power lens as "bright stars," of higher refractility than other cells, especially with the eosin contrast method whereby the background is stained pink whilst cysts stand out as clear refractile objects. Examination should not be considered as completely excluding an amœbic infection until the stool has been searched on each of seven consecutive days. Cultural methods may assist diagnosis in scanty infections.

In cases in which there is any doubt of the identity of the cysts, they may be stained by the rapid, or by the more prolonged iron-hæmatoxylin method. Mixing the fresh fæces with a solution of Weigert's iodine brings out nuclei and other characteristics; concentration methods may

also be applied (see p. 1087).

Charcot-Leyden crystals are commonly found in the fæces in amœbic dysentery, and their presence has been regarded as of diagnostic importance. The crystals vary very much in size, averaging 5–25 μ ; their typical shape resembles a whetstone, and they are soluble in warm water, strong mineral acids, and alcohol. They may also be found in preparations from amœbic ulcers, obtained through the sigmoidoscope (Plate XIII).

The Editor has pointed out the danger of attaching too much importance to Charcot-Leyden crystals as necessarily diagnostic of intestinal amediasis. He has found them in malignant disease of the rectum, mucous colitis, coccidiosis (Isospora hominis), ulcerative colitis, and various helminthic infections (see

p. 541).

Complement-fixation reaction (Craig).—Craig described a technique for the preparation of amœbic antigen and for carrying out this test, which is practically the same as that used for the Wassermann reaction. The antigen is an alcoholic extract of cultures of E. histolytica grown upon a modified Boeck-Drbohlav medium. A rich culture is selected and from this at least 120 sub-cultures are made. Then all the material at the junction of the egg slant with Locke's serum solution is pipetted into suitable tubes, centrifuged and the sediment extracted in the incubator at 37° C. for fifteen days with seven and a half volumes of absolute alcohol. Craig has now published results from 1,000 cases in which diagnosis was checked by the fæces examination. Of those giving a positive reaction (175), E. histolytica or cysts were found in the fæces of 89.7 per cent.

Meleney and Frye have tested the value of complement-fixation in experimentally infected animals inoculated parenterally with amobic extracts. Experimentally infected dogs and monkeys usually gave a positive reaction.

Recently more specific antigens have been prepared by Wright and others using a rich culture of E. histolytica grown in association with Trypanosoma cruzi.

Amœbic hepatitis has to be distinguished from subtertian malaria, acute cholecystitis, gallstone colic, or empyema of gallbladder. To those unfamiliar with the vagaries of amœbiasis the acute onset with pain may suggest rupture of a peptic ulcer. Differentiation of amœbic typhlitis from acute appendicitis, or appendix abscess, sometimes presents difficulties. For many reasons operation is undesirable in uncomplicated amœbiasis. Appendicitis is, however, a not infrequent sequel of amœbic dysentery. In amœbic typhlitis the X-ray appearances by barium enema assist. The cœcum is distorted and there are usually filling defects. Tenderness is

diffuse, not localized directly over McBurney's point and the leucocyte

response not so great as in appendicitis.

Sigmoidoscopic examination.—Amœbic ulceration may extend into the rectal canal, so that sigmoidoscopic examination, conducted without an anæsthetic, usually affords valuable information. Commonly, small yellow ulcers with surrounding hyperæmia are seen, especially in the region of Houston's valves. It is often possible to demonstrate living entamœbæ in the scrapings, even when they cannot be found in the fæces.¹ In contrast to chronic bacillary dysentery instrumentation is practically painless. Amœbic ulcerations may be touched or scraped

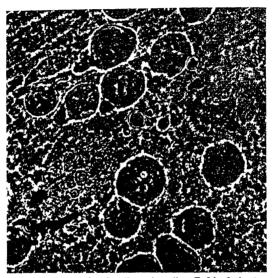


Fig. 71.—Amœbic dysentery, showing tissue-invading E. histolytica in scrapings of ulcer obtained through the sigmoidoscope.

without causing any painful sensation. The mucous membrane surrounding individual lesions shows absence of inflammation, preserves its normal pink colour, but it is usually more reticulated and folded than normal. Amœbic lesions are then seen in the crypts between the folds, either as small, yellow elevations the size of a pin's head, or as superficial snail-track ulcers with hæmorrhagic margins (Plate XIII). Large ulcers are rare. The unit of ulceration is a flat, shallow depression, with undermined edges, and of irregular diamond shape. Often the only signs of abnormality are small, flame-shaped hæmorrhages, in the centre of which entamebæ may be demonstrated in scrapings obtained by means of a long-handled Volkmann's spoon passed through the sigmoidoscope (Fig. 71). A porcupine quill forms a convenient instrument for transferring material from the spoon to the microscopic slide. American authorities describe an aspiration technique for obtaining material from the bowel for microscopic examination.

¹ By this technique the Editor has diagnosed amorbiasis in a case resembling enteric fever.



Fig. 1.—Acute bacillary dysentery (Shiga infection). Note œdema of mucosa and submucosal hæmorrhages.

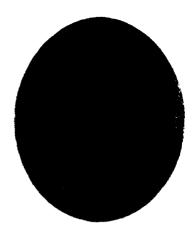
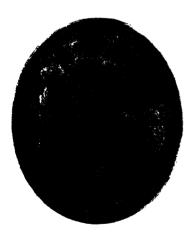


Fig. 2.—Chronic bacillary dysentery Flexner infection). granulations on Note mucous membrane.



Note folding of lax mucous membrane, pin-point ulcers and surrounding submucous hæmorrhages.

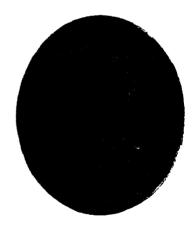


Fig. 3.—Acute amæbic dysentery. Fig. 4.—Chronic amæbic dysentery. Note diamond-shaped ulcers and submucous hæmorrhages.

(P. Manson-Bahr)

SIGMOIDOSCOPIC APPEARANCES OF RECTUM IN BACILLARY AND AMŒBIC DYSENTERIES

In the Editor's series of 535 cases of intestinal amœbiasis, 509 were diagnosed by microscopic examination of fæces, in the remainder by demonstration of amœbæ in scrapings from amœbic ulcers. Out of 258 sigmoidoscopic examinations, amœbic lesions were demonstrated in 234. Morton (1946) has stated a somewhat depressing fact that sigmoidoscopic appearances appear normal in 20 per cent. of proven amœbiasis.

In chronic, partially-healed amcebic dysentery, or even in symptomless cyst-passers, amcebic lesions may be distinguished as minute oval circular pits, or depressions ("pin-point craters"), irregularly disposed. They may be almost microscopic, requiring a magnifying eye-piece for their detection. The surface of the bowel may be peppered with them, giving the appearance of an aerial photograph of bomb craters. The term "pigskin appearance" has been appropriately applied by Cropper to minute scattered pits, resembling pinpricks on a plasticine surface, which persist even after treatment. The Editor regards them as common and most characteristic. Occasionally solitary amcebic ulcers, resembling carcinoma, are seen in the rectum, twenty years or longer after the primary infection. Granulomatous tumours (amceboma or amcebic granulomata) may also be discovered.

Proctoscopy affords an easily performed and less painful method of viewing the rectal mucosa. No special preparation is necessary. A tubular proctoscope about 6 in. long should be employed. The appearances are similar to those already described. Sometimes small granular areas and minute bleeding points can be seen. The Editor now employs this as a routine method aided by biopsy material removed with a special instrument. The cellular picture on microscopic examination gives valuable information. These observations have been confirmed by Jackman and Cooper.

X-rays in diagnosis.—Vallerino described, as indicative of amoebic lesions, filling defects in cæcum and ascending colon with deficient haustration of the bowel, seen after a barium meal, but not so easily after an opaque enema. X-ray diagnosis has been tried on an extended scale at the Hospital for Tropical Diseases, London. Occasionally filling defects have been observed in the cæcum, but similar appearances are seen in other forms of dysentery and colitis. Only unsatisfactory assistance can be obtained by this method. Sometimes when the cæcum is ulcerated the outline becomes ragged and triangular-shaped.

Differential Diagnosis.—Differential diagnosis has to be made from many other conditions in which blood and mucus are passed in the stools, in effect from all other forms of dysentery, colitis, or even other types of intestinal disease. Differential diagnosis from malignant disease of the bowel deserves emphasis, especially when the hypertrophic form of intestinal ameebiasis—ameeboma or ameebic granuloma—is present (see p. 503). Such a tumour is generally sausage-shaped and may reach the size of 12 by 10 cm. and may cause partial occlusion or intussusception. Reliable diagnosis can usually be made by microscopic examinations of scrapings or by removing tissues by biopsy when entameebæ may be demonstrated in sections. This applies especially to the solitary ulcers described above. The X-ray appearances of ameebic hepatitis are very variable, as it is only in upward enlargements of the liver that elevation of the right dome of the diaphragm and restricted movement can be observed on screening. The paradoxical movement of the diaphragm is elicited by Müller's or Hitzenberger's tests. The former—upward

movement of the diaphragm on attempted respiration with closed glottis or nose and mouth—indicates damage to the power of contractility of the diaphragmatic muscles. The latter, produced by short respiration through the nose with mouth closed, is a modification of the former. This causes a short lasting negative intra-alveolar pressure due to respiratory expansion of the thorax with insufficient exchange of air. Blurring of the outline of the diaphragm is probably due to local changes and ædema.

TREATMENT

Many diverse drugs have been advocated for amœbic dysentery. Treatment requires careful supervision. Specific drugs may be preceded by a purge; castor oil being the most suitable. Opium, as a routine measure, should be avoided. The dietary should be carefully regulated and, in the acute stages, nursing is important. As most drugs used in the treatment of amœbiasis contain toxic principles, especially emetine and its derivatives, a definite diagnosis of amœbiasis must be made before they are exhibited. Unfortunately there exists a reprehensible tendency to inject emetine indiscriminately as a diagnostic measure in all forms of dysentery.

I. Emetine.—There are four alkaloids of ipecacuanha but only one, emetine, has definite therapeutic properties. Emetine hydrochloride should be injected subcutaneously or intramuscularly. It is a toxic drug, especially to children and women, when given intravenously, or in excessive doses.

Dobell showed that emetine is lethal to amcebæ in culture, in a strength of one in five million. Nossina proved that this action is influenced by the acidity of the medium. It has a slight action in an acid medium, but the effect increases as the reaction approaches neutrality. The optimum is pH 6.8. Cephæline is far less effective. It is curious that emetine and cephæline, though pre-eminently active in preventing multiplication of E. histolytica, do not apparently exert any direct action. On the other hand, a derivative of emetine—dimethoxyemetine, which has a potent direct action, fails to cure the infection in man.

In large doses, greater than 1 grain a day, emetine is apt to produce toxic symptoms. It has a cumulative action and may lead to asthenia, cardiac irregularity, emaciation, mental depression, and, in rare cases, to myositis or even neuritis which may affect a particular group of muscles and produce partial paralysis, sometimes even atrophy of the scapulo-humeral group, resembling chronic poliomyelitis. Emetine therapy is frequently followed by fine branny desquamation of the skin and atrophic brittle condition of the nails. (Fig. 72.) Emetine by injection exerts no action on the pre-cystic forms of *E. histolytica*.

The effective dosage of emetine seriously overlaps the toxic range. In special study by Brown in the Mayo Clinic toxic effects were recorded in 23 out of a series of 554 cases. Being a cytoplasmic poison emetine is especially toxic when given to patients with bacillary dysentery. Apart from its general action on the tissues, it has an especial affinity for the heart. This action has been shown by Epstein to be on the myocardium and the conducting fibres, and it may even produce auricular fibrillation. Sodeman, D'Antoni and Doerner (1952) have

¹ By electrocardiographic methods Heilig and others have shown that the cardiac effects have possibly been exaggerated.

reinvestigated the subject of intoxication of emetine. They find that the usual dosage of 10–12 gr. in 1 gr. daily doses is perfectly safe for the average patient, but that the optimum dose should be based on a dose/weight ratio of 10 mgm. per kg. weight. There is a great variability of the patient's reactions to emetine. Improperly-conducted emetine injections, especially in debilitated persons, may produce fixation abscesses or widespread cellulitis, and the Editor has seen two cases where this was so extensive that the patient nearly lost his arm. Eczema, or even ulcers, may be provoked at the site of injection. Often the stiffness and irritation resulting from emetine injections are intolerable. Most of these drawbacks may be obviated by giving intramuscular injections.

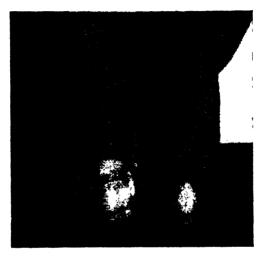


Fig. 72.—Effect of emetine intoxication on the nails: increase of lunule, striation and brittleness. (Dr. T. Jackson.)

It should never be given hypodermically to patients who are leading an active life or taking hard physical exercise. This rule is too frequently disregarded, and permanent damage may result.

It is best to initiate treatment with a course of deep subcutaneous or intramuscular injections of emetine hydrochloride (1 gr. in 1 ml. of distilled water) daily for ten or twelve days. This does not suffice to eradicate the infection from the bowel. It should therefore be supplemented by a course of the double iodide of emetine and bismuth (emetine-bismuth iodide). Emetine injections are much more effective in metastatic amæbic lesions (hepatitis, etc.) than in intestinal amæbiasis. Disagreeable sequelæ may be avoided if the skin is pinched and the needle inserted deep subcutaneously.

The prevailing practice of giving periodic courses of emetine by injection in chronic amcebiasis is subject to serious objections in so far as it tends to render *E. histolytica* emetine-resistant and to make further treatment ineffectual and has probably been responsible for many therapeutic failures during the second world war.

II. Emetine-bismuth iodide was introduced by Du Mez in 1915 and later it was popularized by Dale. It contains 58 per cent. of iodine and 28 per cent. of emetine. In the intestine the insoluble salts of bismuth are converted into bismuth sulphide after passing the pylorus. It is indicated especially in chronic cases and in persistent passers of E. histolutica cysts. More usually known as E.B.I. it is an insoluble powder. from which the emetine is set free by contact with the intestinal juices. It was formerly said not to be decomposed in acid solution (e.g. gastric iuice). but this is incorrect. It passes through the intestinal canal unabsorbed, if compressed into a hard tablet, or if coated with some insoluble substance, such as paraffin, vaseline, resin, keratin, or stearin. It is best made up in powder form in gelatin capsules (Slipules), or mixed with jam or syrup. The maximum individual dose for an adult is 3 gr. (0.2 grm.) per diem for ten to twelve consecutive days, but, if not well tolerated, smaller doses suffice. For delicate individuals and women the dose should commence with 1 gr. and be gradually increased. This drug is more easily tolerated in temperate climates than in the tropics.

The drug is dispensed as a red powder; the capsules of gelatin are manufactured as Slipules. No. 5 size capsule will contain 1 gr. of E.B.I. If the full dose is given, it is better from the point of view of the patient to take one capsule containing 2 gr., but, when treatment is commenced with smaller doses, the patient becomes gradually accustomed to the drug.

If gelatin capsules have been kept for some time they tend to harden and become insoluble. They should therefore be pricked with a pin before being

administered. Sugar-coated preparations are also quite satisfactory.

A more satisfactory preparation (dispersible) has been issued by Burroughs, Wellcome. This diffuses evenly in the duodenal contents, thereby aiding its absorption. The results obtained are more satisfactory than with the original preparations.

It is important to observe certain precautions in giving this drug. When given at 10 p.m., the last solid food should be taken at 6 p.m.; the patient should remain at rest; he should endeavour to go to sleep, and any saliva

should be wiped from the mouth.

Vomiting and diarrhea may occur in the earlier part of the course, and are to be viewed as an indication that the drug is being absorbed. Diarrhea is a necessary prerequisite to cure, because precystic forms of *E. histolytica* live on the mucous surface of the bowel, where they are not affected by hypodermic emetine, but are destroyed in the lumen of the bowel. If no symptoms of nausea supervene, it is probable that the cachets are not being dissolved and their contents freed. It is necessary for the patient to remain in bed and take a liquid or milk diet with eggs and toast.

Excessive vomiting and nausea may be mitigated by 10-15 min. of tinct. opii given half an hour previously, or, in some patients, by nepenthe, luminal, allonal, or chloretone. Most patients lose about 5 lb. in weight

¹ The underlying idea of E.B.I. therapy is that emetine should reach the large intestine unabsorbed. This problem has never been properly solved. Tests for emetine in the urine should be performed after emetine has been given hypodermically or by the mouth. Similarly, faces of patients taking various medifications of E.B.I. should be extracted. Snelling's reaction for emetine consists of adding a few drops of HCl to potassium chlorate, which, with emetine, gives an orange red colour which soon changes to violet.

while under treatment. The condition of the heart and pulse should be noted daily, but treatment should not be discontinued unless depression becomes severe. Almost invariably a fall in blood-pressure (about 20 mm. of mercury) ensues. When the cure is completed the patient should be gradually permitted to resume activity, though dieting (see p. 515) may still be necessary.

For relapsing cases it was formerly considered necessary to give more than one course of E.B.I. and some were thought to be due to amœbæ which had become resistant to emetine. Too much reliance should not be laid on isolated stool examinations, on account of the vicarious appearances of the cysts, but it is advisable to re-examine fæces microscopically at the end of six weeks. The results of treatment are much better controlled by periodic sigmoidoscopic examinations. For some considerable time after disappearance of active lesions, small pits or depressions of the mucous membrane may be seen.

A modification of E.B.I.—emetine periodide (E.P.I.)—is less toxic. It may be given in capsules in dosage of 3 gr. daily, in conjunction with capsules of dried ox-bile, gr. 5, which facilitates liberation of emetine. The Editor favours E.P.I.

for those who cannot tolerate E.B.I.

Auremetine (Willmore and Martindale) is a combination of emetine with auramine (a dye). It is given by the mouth as a dark-maroon powder which is inscluble in water. It is less easily decomposed than E.B.I. in the gastric juice. The dose, 1 gr. in gelatin capsules (slipules), is given four times daily on alternate days for seven days, and then daily until a total of 40-60 gr. has been taken.

III. Iodine-oxyquinoline-sulphonic-acid preparations (Quinoxyl) -Sodium-iodoxy-quinoline sulphate is also known as Chiniofon (B.P.), Yatren (Bayer), Quiniosulphan (May & Baker), Anayodin (U.S.A.) and Dysentulin (German). It is a mixture of four parts of 7-iodo-8-hydroxyquinoline-5-sulphonic acid, containing not less than 26.5 per cent. combined iodine, and one part of sodium bicarbonate. There is some chemical reaction, so that the preparation may contain a small amount of sodium hydroxyquinoline sulphonate, in addition to sodium bicarbonate and iodohydroxy-quinoline sulphonic acid. In solution 100 parts of quinoxyl yield approximately 85 parts of iodohydroxyquinoline sulphonate. Quinoxyl can be given either by the mouth or by retention enema. By the former route the maximum daily dose is 1 grm. (15 gr.) in powder form, in capsules, or keratin-coated pills, for ten days. After an interval of one week this course should be repeated. The drug is excreted in the urine, and can be recognized by the oxyquinoline test (green colour with perchloride of iron). Quinoxyl in pill form (4 gr. each), acts best when acute symptoms of amediasis have been controlled by emetine. The maximum dose is four a day.

Quinoxyl should be given as rectal injections (retention enema), as well as by the mouth. The bowel must first be washed out and cleared of mucus by an enema (1 pint) of 2 per cent. sodium bicarbonate at 8 a.m. One hour later 227 c.c. (8 oz.) of a 2.5 per cent. solution of quinoxyl, in warm water, is introduced through a stout rectal tube. The patient should be encouraged to retain the solution as long as possible, from 8 to 10 hours. The solution is then returned as a greenish liquid containing mucus and débris derived from the bowel. The

 $^{^1\,\}mathrm{A}$ somewhat similar compound is iodochloroxy quinoline or enterovioform, which has proved effective in monkey a meshiasis (Leake).

course of rectal injections is continued for ten days. The course may be repeated two or three times with a week's interval between each. Dieting and rest in bed are absolutely necessary.

IV. Combined or synergistic treatment.—This method of treatment gives permanent results. There have been some relapses in the series, which have been subsequently cured by further treatment. It is assumed that E.B.I. acts on the amcebic lesions in the upper portion of the large intestine, quinoxyl on ulcers and lesions situated in the lower portion. It is necessary that the patient should be at rest and in bed the whole of the ten days of this treatment. Due attention must be paid to the dietary. It is not necessary to give more than a total of 36 gr. of E.B.I. and the maximum individual dose should not exceed 3 gr.

SCHEME OF DIETARY AND COMBINED TREATMENT FOR INTESTINAL AMGBIASIS

7 a.m., pot of tea and 2 oz. milk.

7.30 a.m., one egg, buttered toast, cup of tea and 2 oz. milk.

8 a.m., sodium-bicarbonate enema, 2 per cent., 1 pint.

8.30 a.m., quinoxyl 2½ per cent. by rectum (8 oz.).

9 a.m., 8 oz. milk.

10.30 a.m., juice of an orange, glucose 1 oz.

12 noon, liver soup, chicken or fish, toast, butter, custard or milk jelly, baked apple.

4 p.m., boiled egg, toast, butter, juice of one orange and ½ oz. glucose, grapes or ripe banana, sponge fingers.

5 p.m., quinoxyl enema voided.

6 p.m., 8 oz. milk; bath.

9.30 p.m., sedative (luminal gr. 1).

10 p.m., E.B.I. (gr. 3).

10.30 p.m., sleep.

During combined treatment the patient should be nursed in bed and should be allowed to get up for his bath. He may be allowed to use a night commode for stools and for voiding the residue of the quinoxyl enema. On the first night E.B.I., gr. 1, is given; subsequently, gr. 2 and gr. 3.

After the completion of treatment, the patient must be permitted two days' rest to regain his strength, as a sense of weakness or stiffness is produced in the limbs; but, if carefully carried out, this treatment is not specially exhausting.

Other methods of treatment.—Stovarsol (Acetarsol), an arsenical preparation (3-acetylamino-4-hydroxyphenyl-arsonic acid), containing 27·2 per cent. of arsenic, has been advocated, mainly in France, as an amœbicide, and has been widely used in the treatment of amœbic dysentery in combination with other drugs. It has a feeble amœbicidal action, but stimulating properties. Its special use is in the after-cure of amœbiasis. It is dispensed in 4-gr. tablets, and the maximum dose is two daily for one week to ten days, but not longer; in sensitive persons not more than one tablet daily is advisable. This drug has to be carefully watched, as it may give rise to a toxic erythema with pyrexia resembling German measles, or even to exfoliative dermatitis and a delayed papular toxic rash has been seen three weeks after the administration of the drug. None of these arsenical drugs should be administered to patients in whom liver damage is suspected. Other varieties are known as Spirocid, Orarsan (Boots) and Halarsol (May & Baker).

Carbarsone has been much used in America and is given in the same manner as stovarsol, and has apparently the same therapeutic properties and the same indications. Most American authorities advise a dose of 0.25 grm. twice daily in capsules (pulvules) for ten days. Both stovarsol and carbarsone may be administered per rectum in the form of retention enemata of 2 grm. in 220 ml. of warm 2 per cent. sodium bicarbonate solution. Amibiarson is a similar compound. All these are useful in cyst-passer cases.

Anderson *et al* claim that two trivalent derivatives of carbarsone—dithio-carboxyl methyl and phenyl—are more efficient than the original pentavalent salt. It is thought that the latter is normally converted into the former in the body.

 $\dot{Milibis}$ (Wia) (Winthrop) is a bismuth, derivative of p-N-glycolylarsanilic acid, and contains 15 per cent. arsenic in pentavalent form and 41·88 per cent. bismuth. It has an action rather similar to that of carbarsone, but is, however, less soluble and has acquired a very considerable reputation in the treatment of chronic ame biasis especially in emetine-resistant cases. The tablets, of 250 mgm. each, are given two to three times daily for seven days. It appears to be particularly non-to-xic. (Milibis is amebicidal in dilution of 1:1000 to 1:2500.) Although it contains 15 per cent. arsenic and 42 per cent. bismuth, these are split off so slowly and incompletely that it is almost impossible to kill animals in toxicity experiments. Only 2 per cent. of the arsenic is excreted in the urine.

Vioform, or enterovioform (iodochlorhydroxyquinoline), is somewhat similar to iodoform and contains 37.5 per cent. of iodine. It is administered by the mouth in gelatin capsules each containing 0.25 grm. (4 gr.) of the powder, three times daily, for ten days. In chronic cases it may be injected for ten days as retention enemata, consisting of 150–200 ml. of warm water in which 2 tablets have been dissolved.

Diodoquin, Diiodohydroxyquinoline, Dihaloquin, Savorquine, or Embequin contains 63.9 per cent. iodine, and was first introduced in 1935 by Craig and d'Antoni. Its action is similar to that of vioform and has proved itself a valuable drug. It has very definite amæbicidal action, but is not satisfactory in the active stages of amæbiasis, though of great assistance in clearing up symptomless cyst carriers. In a few cases it causes pruritus ani. Tablets of 3.2 gr. are given by the mouth. The customary dose is 8 tablets daily for 15 days.

Conessine, the alkaloid of kurchi bark (Holarrhena floribunda), which was formerly used in India for the treatment of amœbiasis, has once more come to the fore. French writers are unanimous in its praise and consider that it will replace emetine. Criticisms are being levelled at its widespread use on account of its toxicity to the nervous system, and its ineffectiveness in hepatic amœbiasis. (Lavier, Crosnier and Merle.) Porte uses it especially in amœbic dysentery cases which are resistant to emetine and Merle found it most successful in children. Conessine in tablets of 0.5 grm. is given three times daily for a total of 5.5 grm. An important drawback to this treatment is its liability to produce alarming psychotic upsets. Kurchi bismuthous iodide (Anabin) contains the total alkaloids of the bark, is given in 10 gr. doses twice daily for 10 days without producing undue disturbance.

Antibiotics in Treatment of Amæbic Dysentery.—Aureomycin has been shown to exert an action upon E. histolytica in culture (see p. 921) but most authorities (Anderson, Bradin and Hansen) suggested that aureomycin is not directly amæbicidal when tested out on 52 African cases, five of which were of exceptional severity. The first effect is to lower the number of stools and to reduce the bacterial flora. The dose employed is 0-25 grm.

four times daily (1 grm.) for 15 days. Treatment is controlled by daily sigmoidoscopy which reveals rapid granulation; twelve, for instance, were completely healed by the fourth day. Diarrhea ceased in 1–2 days. Disappearance of amœbæ was not only rapid, but dramatic. The effect was, however, temporary, because the relapse rate was high within two weeks of cessation. Armstrong, Wilmot and Elsdon-Dew (1950) in Africans gave 0.25 grm. four times daily at six-hour intervals for 15 days. Daily sigmoidoscopy showed remarkably rapid healing. Disappearance of amæbæ was equally rapid, but relapse rate was high. McVay has given larger doses totalling 19–22.7 grm. in doses of 0.5 grm., four times daily, when blood levels were estimated at 8 m μ per cent. and final results satisfactory.

Bacitracin.—Recent work on this antibiotic is by Most and colleagues. His results were encouraging, resulting in clinical cure and the rapid disappearance of E. histolytica from the stool. The daily dose varied from 40,000 to 120,000 units by mouth and was continued for 5–20 days. Eventually the course was standardized at 80,000 units daily for 10 days. Sixty-six per cent. of cases were cured after one treatment, but the relapse rate was high; however, further treatment resulted in the cure of another 33 per cent. Bacitracin has therefore been rated as an important addition to the list of anti-amœbic drugs.

Terramycin.—This new antibiotic has been introduced into the treatment of amœbiasis and has received some favourable comment. Sanchez and colleagues in Mexico found that 40 mgm. per kg. for 4 days resulted in a satisfactory cure. Most and van Assendelft (1951) have used it on a much more extended scale with doses of 1 grm. for children and 2 grm. for adults daily for from 5 to 10 days. Out of 37 persons treated with a full course all, but one, remained free from parasitic relapse. Terramycin appears to be the most active of all the antibiotics so far introduced in treatment of amœbiasis. Crosnier and colleagues (1951) have treated 17 patients from Indo-China with rather larger amounts of the drug; 3 grm. daily for 5 days and then another 2 grm. daily for a similar time. The clinical response was said to be spectacular. Finally they state that terramycin frees 100 per cent. of patients of E. histolytica: aureomycin 60 per cent. and bacitracin 28 per cent.

Fumagillin.—An antibiotic isolated from aspergillus culture (Hanson and Eble) was found unexpectedly to be a potent amœbicide. McCowen and colleagues have demonstrated that it can inhibit a strain of E. histolytica, in association with a mixed bacterial flora, in dilutions as high as 1 in 130 million. In rats cæcal infections are cleared up by administration of 11 mgm. of fumagillin per kg. body-weight in the space of two days. In monkey amœbiasis fumagillin is very active (Hrenoff and Nakamura).

General observations on antibiotics.—Elsdon-Dew and associates (1952) have produced the most complete investigation upon the effect of antibiotics in acute amœbiasis.

It was thought that the main action of antibiotics was on organisms other than the amœba, but now there is evidence that aureomycin and terramycin have some direct anti-amœbic effect, but against this it has been shown that

the former drug has such effect on these organisms in amœbic abscess or in amœbic hepatitis. One great feature of the antibiotic treatment is the rapidity with which the lesions heal and the amœbæ disappear. With aureomycin 1 grm. daily in divided doses, on the tenth day 67 per cent. of cases had been cleared of their ulcers and 98 per cent. of their amœbæ: with terramycin in the same doses, 84 per cent. and 94 per cent., respectively. Procaine penicillin and succinyl sulphathiazole appear to have a synergistic effect and were much more successful than in combination with other sulphonamides. With all these antibiotics early relapses after 4–8 weeks are usual. Other established amœbicides should therefore be given in conjunction.

Results with chloramphenicol, bacitracin, streptomycin and neomycin were not so satisfactory. With all antibiotics acute dysenteric cases may be converted to symptomless cyst carriers.

Treatment of hepatitis.—During the course of amœbic dysentery, and for months afterwards, the liver must receive careful attention. It may not be possible to prevent abscess formation; but if pain suggests, an attempt to avert this grave complication may be made by giving repeated doses of emetine subcutaneously, saline aperients, rest, low diet, fomentations, dry-cupping, and similar measures. Emetine acts much more rapidly and specifically in hepatitis than in amœbic infection of the bowel, and in some cases aspiration of the liver (hepatic phlebotomy) has a wonderful effect. Usually a total of 6 gr. of emetine suffices to overcome the more active symptoms and should be followed up by chloroquine (see p. 531).

Perforation of amæbic ulcer.—To avoid fatal peritonitis, diagnosis of perforation of the large bowel should be made as soon as possible. The difficulties have been emphasized by James during the recent war in five cases of perforation of the cæcum and colon. The time factor is of supreme importance. Fæcal fistulæ are apt to form. When perforation occurs in a fixed portion of the colon it can be closed and covered with omentum. The difficulty of making silk sutures hold is emphasized.

Strictures may sometimes form in chronic cases, almost invariably at a level of two inches above the anal canal. Early cases are crescentic in outline, later becoming annular or diaphragmatic.

Amæbic appendicitis and typhlitis.—If operation is undertaken, the minimum and most gentle handling of the bowel is necessary. It must first be determined whether the condition of the cæcum is secondary to that of the appendix or vice versa. If the appendix is removed the abdomen is closed with a soft corrugated drain which is left in for 72 hours.

Diet.—A suitable diet in the convalescent treatment of amœbic dysentery is important. Alcohol, unless taken in small quantities, certainly predisposes to relapse. The following diet is advocated for four weeks after active treatment:

Permitted.—Porridge; eggs; filleted or fried fish—haddock, plaice, cod, sole or whiting; toast or rusks; milk puddings—rice, sago, semolina, ground rice; spinach or young peas, vegetable marrow, cauliflower; plain cakes; fruit jellies; stewed pears or peaches; baked apples; bananas, grapes; tripe, brains, sweetbreads; chicken; rabbit; game.

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Not permitted.—Cheese; new bread; potatoes; fats; suet puddings; rich cakes with raisins or spices; pastry; pickles.

Meat.—Red meat, i.e., mutton or beef, can be permitted once daily.

Surgical measures must be reserved for complications of amœbiasis, such as pericolic abscess. Dunlop (1946) has written a vivid description of the appalling severity of amœbic bowel lesions in Japanese prison camps. The surgical cases fell into two groups. The acute cases, in which the principal difficulty was relief of pain, tenesmus and wasting were much benefited by appendicostomy and cæcostomy. Chronic cases with grossly damaged colons, which had failed to respond to anti-amœbic treatment, were subjected to ileostomy and the results were dramatic in 14 cases. Theron (1947) points out that the mortality rate in operations on intestinal amœbiasis is considerable, due to decreased resistance, hypoprotinæmia and interference with wound healing. Moreover, as the result of operation, acute amœbic dysentery may develop.

Modern views on treatment.—In the twenty years which have elapsed between two great wars during both of which very large numbers of men were infected with amcebic dysentery the results of treatment of intestinal amœbiasis with a combination of emetine bismuth iodide and quinoxyl were considered eminently satisfactory. A proportion of cases relapsed within a comparatively short period after E.B.I. therapy, and since 1945 unsatisfactory results have been frequent. The amoba (E. histolytica) appear to be often refractory to emetine, although experimental evidence is inconclusive. It was suggested that, in response to repeated courses of emetine injections, the organisms become emetine-fast. In consequence, many combinations of treatments have been introduced. In 1945 Hargreaves and others suggested that this might be attributed to secondary bacterial infection of diffuse and generalized ulceration of the bowel in debilitated, emaciated and fever-stricken soldiers. In a small proportion of these patients intensive therapy with penicillin and sulphasuccidine was followed by remarkable recovery, though the amœbic infection persisted. This has led to the general adoption of the view that treatment with these bactericidal agents is an essential preliminary to emetine therapy. There is, however, no certainty that such an invariable bacterial infection coexists and it is admitted that there is no proof that this much more complicated and prolonged course is more successful than the simpler synergistic treatment described above. In emetineresistant cases one of the arsenical drugs, such as Milibis, is frequently successful.

Prophylaxis of amediasis is practically the same as for bacillary dysentery, and depends upon efficient sanitation, measures directed against the housefly, and avoidance of unboiled water, raw vegetables, or other foods which may have been contaminated by human fæces. As cysts of E. histolytica can only survive in a moist medium, there is a considerable amount of evidence, experimental and epidemiological, that amedic infection is usually waterborne. The problem of dealing with human carriers of E. histolytica cysts is a constant difficulty. It is not likely to arise in countries equipped with a proper system of sanitation,

but in no case ought a cyst-carrier to be employed as cook or mess orderly, or handle water supplies.

Water contaminated by E. histolytica cysts should be treated as follows:

- (1) Heavy dose of aluminium sulphate at the rate of 6-10 gr. per gallon.
- (2) Allowed to settle for 1 hour.
- (3) Filtered at a rate not to exceed 6 gallons per sq. foot of filter surface per minute.
- (4) Finally chlorinated.

For small-scale water supplies, the greatest amount of protection is provided by filtration through diatomaceous silica after previous sedimentation.

Quinoxyl, in pill or tablet form (4 gr.) at night, wherever amœbiasis is rife, acts as a prophylactic measure. Diodoquin is also recommended and a combination of chloroquine, 250 mgm., and milibis, 75 mgm. (Berberian).

COMPLICATIONS OF AMERICAN

1. HEPATIC ABSCESS (LIVER ABSCESS; HEPATIC AMCEBIASIS)

Geographical distribution.—Liver abscess of the type known as tropical abscess, for the most part a disease of warm climates, corresponds in its distribution with amediasis. While the entameda is the principal element in its production, its incidence depends probably on special susceptibility of the European to this complication.

Attology. Relation to amæbic dysentery.—There can be no question of the existence of an intimate relationship between amæbic dysentery and liver abscess. Many well-authenticated statistics, as well as everyday experience, attest this. In 3,680 dysentery autopsies made in various tropical countries, and collated by Woodward, 779 (21 per cent.) revealed abscesses of the liver. Extensive amæbic ulceration may exist without exciting any subjective symptoms (see p. 498). Moreover, many patients suffering from liver abscess forget, or fail to mention, a previous dysenteric attack, or may mislead the physician by describing such an attack as "diarrhæa," so that the relationship is much more intimate than even statistics indicate. In the great majority of cases dysentery antedates the abscess, it may be by as long as twenty years.

Race, sex, and climate.—Though common in Europeans in the tropics, liver abscess is proportionately rare among natives. Thus, in the native army of India the proportion of deaths from liver abscess to the total mortality in 1894 was only 0.6 per cent., whereas in the British army it was 7.4 per cent. Man for man, the relative liability of the European and the Indian soldier was as 95.2 to 4.8. This disproportion holds in spite of the fact that a larger proportion of the natives are infected with E. histolytica.

It is well known that European women in the tropics, though nearly as subject to dysentery as European men, rarely suffer from liver abscess, and children hardly ever. It is most common between the ages of 20 and 40, though there are records of ameebic abscesses of the liver in Egyptian children of three months of age and of others in India of ten. The youngest in the Editor's experience was an English girl of sixteen.

Pathology.—It may be inferred from the symptoms that in the early stages of suppurative hepatitis there is general congestion and enlargement of the liver: in some instances this condition may be more or less confined to one lobe or even part of a lobe. Later, as shown especially by observations on cases that have died from the attendant dysentery, one or more greyish, ill-defined, circular patches, 1-1 in. or thereabouts in diameter, are formed. These grey spots are very evident on section. A drop or two of a reddish, gummy pus may be expressed from these necrotic patches. Still later, the centres liquefy, and distinct but ragged abscess cavities are formed. An abscess thus commenced extends partly by breaking down of liver parenchyma; partly by more massive necrosis of portions of its wall; partly by the formation of additional foci of softening in the neighbourhood, and subsequent breaking down of the intervening septa. The walls have a ragged and tessellated appearance. As the abscess enlarges, so the zone of necrotic tissue becomes narrower. The character of the contained pus also changes during the evolution of the abscess; it frequently becomes secondarily infected with streptococci and other organisms, when it assumes a brownish or greenish colour.



Fig. 73.—Multiple liver-abscesses from a case of acute amoebic dysentery, showing characteristic structure and zone of acute hyperæmia. Quarter nat. size.

Carrera suggests that the shape and appearance of affected liver areas are of vascular origin, resembling infarcts. Wherever amoebæ are detected in one of the larger branches of the portal vein there are small collections of fibrin filaments and leucocytes in the vicinity. Probably amoebæ form the nucleus round which thrombi develop.

Number, size, and situation of abscesses.—Liver abscess may be single or multiple. If multiple, there may be two, three, or many. When single, the abscess sometimes attains a great size. Frequently it is as large as a coco-nut, or even larger; the entire liver even, with the exception of a narrow zone of hepatic tissue, having been converted into a huge abscess sac. When multiple, the individual abscesses are generally smaller, ranging from the size of a filbert to that of an orange (Fig. 73).

As might be expected from considerations of the relative size of the parts, single abscess is much more common in the right than in the left smaller lobe. The upper part of the right lobe might be termed the seat of election. Compensatory hypertrophy of the left lobe is commonly produced if there is great destruction of the right.

Adhesions to surrounding organs are frequently, though not invariably, formed as the abscess approaches the surface of the liver. In this way the danger of intraperitoneal extravasation is usually averted.

Intestinal ulceration usually co-exists; it may be very extensive, or confined to a few small punched-out ulcers, generally in the neighbourhood of the cœcum. Or, again, there may be no visible lesions of the mucous surface.

Pulmonary inflammation and abscess f om escape of liver pus into the lungs are sometimes discovered post mortem. Generally the pulmonary abscess communicates with the mother abscess in the liver by a small opening in the diaphragm, the pleural sac being shut off by adhesions. (Plate XVI.)

Liver pus.—The naked-eye appearance of liver pus is peculiar, almost characteristic. When newly evacuated, it is usually chocolate-coloured, streaked, or mixed, with larger or smaller clots or streaks of blood, and here and there with streaks of clear mucoid yellowish material. It is so viscid that it will hardly soak into the dressings, lies on the surface of the gauze like treacle on bread, spreading out between the skin and the dressing, and finding its way past the edge of the latter rather than penetrating it. When quite fresh, here and

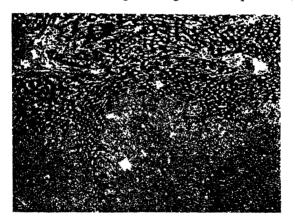


Fig. 74.—Structure of miliary amoebic hepatic abscess containing E. histolytica. (Photomicrograph Dr. C. J. Hackett.)

there, little islands of what may be described as laudable pus may be made out in the brown mass. Sometimes it contains considerable pieces of necrotic tissue. Occasionally, also, from admixture of bile, the abscess contents are green-tinged; they are rarely offensive, unless the abscess lies near the colon. Under the microscope many blood-corpuscles are seen, besides much broken-down liver tissue, large granular pigmented spherical cells, lecithin plaques, leucocytes, débris, oil globules, hæmatoidin, occasionally cholesterin, Charcot-Leyden crystals and sometimes entamcebæ. Cysts of *E. histolytica* are never found.

Entamæbæ and other organisms.—In Egypt, India, and elsewhere entamæbæ may be detected in half the cases. Usually they cannot be found in fresh liver pus, either aspirated or escaping during operation, but they appear, often in great profusion, four or five days later in discharges from the drainage-tube. They may occur in strings of eight to ten. Unless the patient is treated with emetine, the amœbæ may persist in the discharge until the abscess has healed. The Editor has succeeded in growing them on Drbohlav's selective medium when they were not apparent in the pus. The longer the abscess has persisted the larger its size, and the more difficult it is to find amœbæ (Fig. 75). The pus is bacteriologically sterile, but occasionally may become secondarily infected by Bact. coli, hæmolytic staphylococci, streptococci and Salmonella enteritidis, in which case the

entancebæ in the liver pus are destroyed. There is some evidence that in the majority the secondary bacterial infection is derived from the bowel, more rarely

from the lungs.

Encystment.—In rare instances liver abscess pus, instead of being chocolate-coloured and viscid, is yellow and creamy, particularly when the abscess becomes encysted. The walls are thick, smooth and fibrous. In the course of time the contents become cheesy, and ultimately cretified until the cyst shrivels up and contracts (see Plate XV). Calcified abscesses are occasionally found by radiography, and do not give rise to symptoms. They have to be differentiated from calcified hydatid cysts and sometimes also from calcified suprarenals.

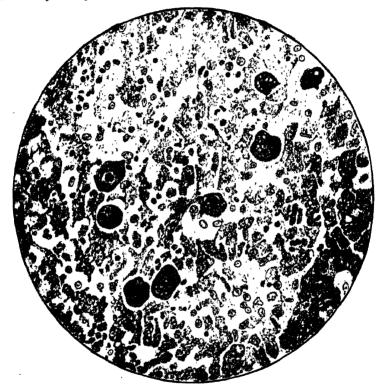
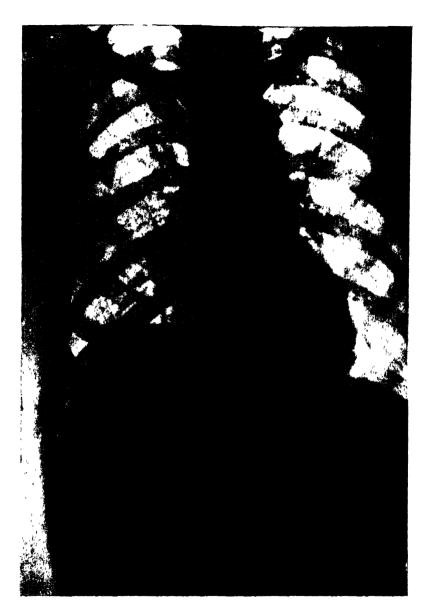


Fig. 75.—Microscopical section of liver abscess, showing Entamaba histolytica at margin of abscess cavity surrounded by necrotic liver cells.

Bilaterality of the liver.—Until recently it was considered that no differences existed between the right and left branches of the portal vein, the hepatic artery and the hepatic ducts, although the right lobe of the liver is treble the size of the left. Cantlie in 1884 first noted hypertrophy of the left lobe of the liver consequent upon total destruction of the right. On this account, and also on account of the embryological development, it was suggested that the generally accepted anatomical division of the liver was incorrect and that it should be divided, not by the antero-posterior fissure, but by a line drawn from before backwards through the fundus of the gall-bladder to the spot where the anterior vens



Radiograph of dome of diaphragm in liver abscess.

(Dr. Carmichael Low.)

LIVER ABSCESS

PLATE XIV



Radiograph of cretified abscess in right lobe of liver. (Radiograph by Dr. M. Cordiner.)

LIVER ABSCESS

PLATE XV

cava grooves the back of the liver; this is the mid-line of the liver. This view is borne out by pathological studies and the results of injection of the portal and hepatic veins and hepatic artery (McIndoe and Counseller). Copher and Dick (1928) demonstrated that the distribution of the portal streams in the liver of the dog can be determined by injections of trypan blue, and that there are at least three distinct and separate currents (streamline phenomena) in the portal vein. Hypertrophy of the left hepatic lobe ensues upon partial or complete destruction of the right, a feature of considerable importance in diagnosis.

The genesis of liver abscess.—Amœbic abscess of the liver appears to be the result of portal embolism from amœbic ulcers in the bowel. According to Rogers, this focus is usually in the right sector of the abdomen, either in the cœcum or ascending colon; this fact, therefore, accounts for the common situation of such an abscess in the right hepatic lobe. Direct infection of the anterior surface of the liver may possibly take place from an amœbic ulcer in the hepatic flexure, via the peritoneum, but there is no evidence to show that this constitutes the usual method.

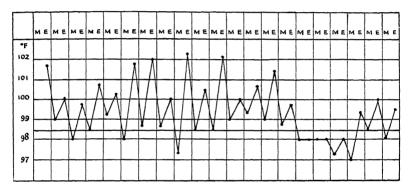


Chart 23.-Amæbic abscess of liver.

In amæbic hepatitis, which is probably the precursor of amæbic abscess, there appears to be a massive amæbic portal infection. Probably the great majority of the organisms are destroyed by resulting tissue-reaction; survivors multiply and cause necrosis of the surrounding liver cells and thus constitute the starting point of a liver abscess. Cytolysis is brought about by the rapidly multiplying amæbæ; but ultimately the amæbæ themselves are destroyed by the products of their own activity. Sterile amæbic abscesses at this stage are particularly liable to secondary infection with pyogenic and other organisms. As originally pointed out by Councilman and Lafleur, the primary lesion is central necrosis of the liver lobule, a prelude to subsequent abscess formation.

Symptoms.—There is great variety in the symptoms of liver abscess. As a general rule, the patient is one who has long resided in the tropics and who at some time or other has suffered from subacute attacks of dysentery. At first he becomes conscious of a sense of weight and fullness in the right hypochondrium, and later suffers from sharp stabbing pains over the hepatic area, accentuated by coughing.

Shoulder pain.—In a considerable proportion of cases a sensation of uneasiness or rheumatic pain around the right shoulder-joint is complained of, especially at night. Usually this is referred to the acromial region (appropriately termed, "the liver wing"). It is due to reflex irritation of the phrenic nerve, transmitted through the fourth cervical root from which the supra-acromial and supra-clavicular cutaneous nerves originate in the cervical plexus, and is comparable to that of diaphragmatic pleurisy or gall-bladder disease. In left-lobe abscess pain is generally referred to the left shoulder-joint.

General features.—Soon the patient becomes feverish, particularly towards evening, and may experience a few short rigors. He begins to lose flesh, and his complexion assumes a yellow, muddy tinge. A quotidian fever now becomes a regular feature, every evening reaching 102° F. (rarely

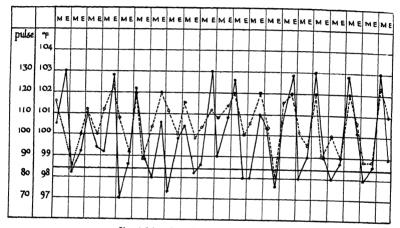


Chart 24.—Amoebic abscess of liver.

Hectic fever with tendency to tertian periodicity. Dotted line = pulse-rate.

higher), and sinking to below normal in the morning (Charts 23, 24). The pyrexial bouts are accompanied by profuse sweats, necessitating frequent changing of clothing during the night. The patient is emaciated, his tongue furred, the extremities cold and clammy; breathing is shallow and mainly thoracic. Sometimes swelling in the epigastrium may be observed over the site of the abscess. Discomfort or deepseated pain may be produced by palpation and deep percussion over the right hypochondrium. The lower border of the liver is usually enlarged below the costal margin; sometimes, but less frequently, it extends upwards an inch above the normal, while posteriorly the duliness can be detected from the angle of the scapula to the costal margin. It may be further observed that the upper line of dullness is arched, and is altered by changes in position, when the patient lies on his left side or when he stands up. Deep inspiration may give rise to acute pain, and sometimes one or two tender points may be discovered in the lower intercostal spaces. The spleen is not enlarged. On auscultation, pleuritic rubs may be detected



Radiograph of liver abscess bursting through the diaphragm into base of right lung, whence the pus is being evacuated through a branch of the right bronchus. A—collection of pus in pleural cavity; b—valve-shaped opening through diaphragm at site of abscess in liver. (Radiograph by Dr. M. Berry.)

LIVER ABSCESS

at the base of the right lung, or signs of compression, such as inspiratory crepitations, decreased breath-sounds, or diminution of vocal fremitus may be noted at the base of the right lung (Fig. 76). Pain is usually relieved by lying on the affected side (Fig. 77).

In abscess of the left lobe a tumour of variable outline, sometimes resembling in shape and position an enlarged spleen, may be felt in the epi- or hypogastrium. Usually there is some compression involvement of the base of the left lung, but it must be remembered that such a tumour may arise from compensatory hypertrophy of the left lobe.

As the case progresses, so the patient becomes more emaciated; hectic fevers with drenching nocturnal sweats continue; liver dullness and pain increase; or general enlargement may subside, and percussion

reveal a local bulging in an upward or downward direction. If the abscess which has now formed is not relieved, the patient may die worn out after months of illness; or the abscess, having attained great dimensions, may burst into the right lung or pleura, or even elsewhere, and be discharged with either recovery, or death from continued hectic fever and exhaustion, or from some intercurrent complication. (Plate XVI.)

The blood shows a well-marked leucocytosis of 15,000-35,000, though in some rare cases there may be no appreciable rise. The mean average of the differential count in the Editor's series of cases is 70-8 per cent. polymorphonuclears; 22-2 per cent. lymphocytes; 6 per cent. large mononuclears; and 1 per cent. eosinophils. With liver abscess of long standing there is usually



Fig. 76.—Clinical picture of liver abscess, showing enlargement of liver and bulging of chest wall.

severe secondary anæmia, and occasionally the blood changes may assume features of the pernicious type.

In two cases of hepatic abscess recorded by the Editor the serum agglutinated Sal. enteritidis in high titre, with co-agglutination of Sal. typhi, and the former organism was isolated from the abscess pus as well as from the fæces.

Great variety in the urgency of symptoms.—Although the foregoing is a fairly common history in liver abscess, there are many instances in which the initial symptoms are much more urgent and the disease progresses much more rapidly. In other instances subjective symptoms are almost entirely absent, or so subdued that the true nature of the case may be entirely misapprehended until the abscess bursts through

¹ Occasionally an eosinophilia has been recorded in association with liver abscess.

the lung or bowel, or a fluctuating tumour appears in the neighbourhood of the liver; or, perhaps, until the unsuspected abscess is discovered on the post-mortem table.

Sometimes the initial fever is high, and persists for a considerable time, but later it usually becomes distinctly quotidian and intermittent; sometimes temperatures of 103° and 104° F. may be recorded. There is not one

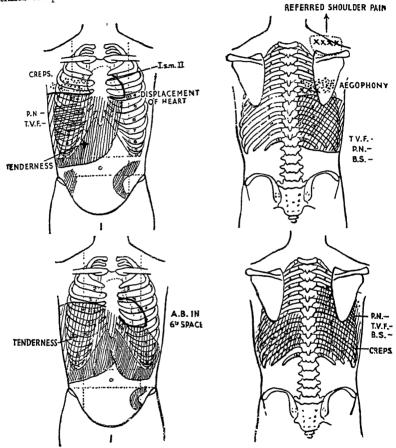


Fig. 77.—Physical signs of liver abscess.

Above-Of right lobe of liver, cured by aspiration with Potain's aspirator.

Lencocytes, 9,000; E. histolytica cysts in fæces. I.s.m. II, basal systolic murmur; P.N.—, percussion note diminished; T.V.F.—, tactile vocal fremitus diminished; B.S.—, breath-sounds absent; OREPS., crepitations.

Below-With hypertrophy of the left lobe, cured by aspiration of 65 ounces of sterile pus.

Leucocytes, 12,000; E. histolytica cysts in fæces. A.B. apex-beat; P.N.—, percussion note diminished; T.V.F.—, tactile vocal fremitus diminished; B.S.—, breath-sounds absent; OREPS., crepitations.

single cardinal sign which may not be absent in hepatic abscess; thus, large collections of pus have been noted unaccompanied by fever. Marked rigors are rare but, when present, indicate threatened rupture through the diaphragm or into some viscus. Sweating accompanying the pyrexia usually takes place about the head and neck. Enlarged cervical and axillary glands on the affected side may sometimes be noted, while rheumatic-like pains in, or swellings around joints, and clubbing of fingers have been described. Pain of some description is rarely absent. Usually, a sense of fullness and weight in the region of the liver, or referred to the infrascapular region, is complained of; stabbing and stitch-like pains may be increased by pressure, and especially by deep inspiration or coughing. Localized painful areas usually occur below the costal margin, and indicate that the abscess is pointing in that direction. Pain on swallowing, when the bolus traverses the lower end of the œsophagus, has been recorded. Pain on firm pressure with the finger-tips in an intercostal space, and over a limited area, is a common and valuable localizing sign. Shoulder pain, in about one-sixth of the cases, may be. the only symptom and may be noted before the advent of fever.

Attention may also be drawn to the respiratory symptoms; a painful cough, possibly due to reflex irritation of the diaphragm, may be prominent, while the respiration may be rapid and shallow. The patient usually lies on his back, inclining slightly to the affected side; if the abscess is on the right, lying on the *left* side becomes distressing owing to adhesions,

or possibly to pressure on the heart.

The tongue is generally furred, the digestion disturbed; flatulence and diarrhea are frequent. There may, but infrequently, be concurrent amedic dysentery with blood and mucus in the stools.

The heart may be displaced laterally or upwards by pressure of a large abscess. Tachycardia and cardiac irregularities may result from toxic

absorption or from pressure.

Rigidity of the upper part of the right rectus muscle may be noted if the abscess is situated in the vicinity of the gall-bladder. Percussion, besides eliciting tenderness and causing pain, may convey to the examiner a sensation of ballottement as of percussing a thick-walled elastic bag filled with air. The right upper superficial reflex may be diminished or absent.

Swellings in the epi- or hypogastrium closely simulate intra-abdominal tumours, and in apyrexial cases of hepatic abscess their nature may not be suspected until they have been aspirated. There may be varicosity of the epigastric veins. Local *cedema* over one or more intercostal spaces is sometimes apparent; local *bulging* usually indicates the site at which the abscess is pointing (Fig. 77).

Friction rubs, pleuritic or peritoneal, may sometimes be found; while pneumonic signs at the base of the right lung indicate contiguity of the abscess to the diaphragm. Œdema of the feet occurs in advanced cases.

The urine may contain albumin as the result of chronic pus-absorption. When considerable destruction of hepatic substance has taken place, the amount of urea is diminished and that of ammonia increased.

Jaundice is not by any means common; when deep it may be caused

by pressure of an abscess of the caudate lobe on the common bile duct. Toxic jaundice is sometimes met in secondarily infected abscesses, or may be due to coexisting infective hepatitis. Quite commonly, however, there is a subicteric tint with slight yellow tingeing of the conjunctivæ.

The abscess may rupture into any contiguous organ, thereby producing spontaneous cure; generally it ruptures into the lung or pleura. When into the lung, the abscess contents may be suddenly coughed up in mouthfuls of frothy pus and blood; but usually this process is much more gradual and a few drachms are coughed up at a time, but in favourable cases the amount of expectoration gradually diminishes. Amœbic abscess of the lung—resulting from trans-diaphragmatic rupture—is apt to be mistaken for pulmonary tuberculosis. Amœbæ are only exceptionally found in the expectorated pus, but usually striated muscular fibres from the diaphragm may be recognized.

Expectorated liver-pus is usually characteristic, being chocolate-brown

and particularly viscid.

Arrest of the discharge may not necessarily indicate recovery though cessation of the cough may be followed by rise of temperature and reappearance of night-sweats. Alternate emptying and refilling of the abscess cavity may recur many times before final recovery. In some cases expectoration never ceases, and is accompanied by other signs of pulmonary absorption, such as respiratory distress and clubbed fingers. Sudden rupture is often accompanied by the passage of melænic stools.

Rupture into the *pleura* may lead to pleural effusions, which may simulate empyema. Aspiration of these cases may yield clear yellow and highly albuminous pleuritic fluid. Pneumothorax may sometimes

ensue.

Hepatic abscess may rupture into the stomach, causing vomiting of pus; into the bowel, causing diarrhea and discharge of pus in the fæces; or, with fatal results, into the pericardium or peritoneum. Pericarditis, from close contact with intrahepatic suppuration, has also been recorded. A child of twenty months was seen in New Zealand in 1950 with amedic pericarditis. The classical signs and symptoms were present and in the pericardial sac pus containing actively motile E. histolytica was aspirated. The liver did not appear to be involved. The infection had been contracted from the father who had suffered from amedic dysentery. A somewhat similar case has been recorded by Hartz (1950) from the sudden perforation of a left hepatic abscess into the pericardial cavity. The changes in the electrocardiogram were characteristic of pericarditis (a review of the literature on this rare complication is given by Carter and Korones, 1950).

Rupture into the gall-bladder, bile-ducts, hepatic veins, portal veins, inferior vena cava and pelvis of the right kidney have also been reported.

Finally, spontaneous rupture may take place through the abdominal wall, and the abscess, by tracking along the round ligament, may empty itself. The surrounding skin may thus become infected with amœbæ.

From a study of 50 cases of amoebic abscess under the Editor's care it has been possible to set out the following table:—

				1	To. 6	of patients.
History of previous dysentery						30
Entamæba histolytica or cysts in fa	eces					23
Shoulder pain, right						22
" , left						3
Pyrexia, intermittent .						39
" remittent typhoid-like						4
" sudden onset, with rigors	3					2
Pyrexia absent						7
Night-sweats						40
Dysenteric infiltration of bowel—						
Sigmoid flexure						12
Cæcum and sigmoid .						4
Enlargement of liver, upwards						12
" " downwards						38
Pain and tenderness in liver.		_	_			24
Displacement of heart .	_	-		_		4
Associated signs at base of right l	บทฐ		_			38
Pleuritic rub						6
Rupture of abscess into lung						6

Mortality.—Formerly the case-mortality was high, 50–80 per cent., but at the present day, chloroquine and emetine, recognition of the intimate connection of liver abscess with amoebic dysentery, and improved methods for the evacuation of pus, have brought the mortality-rate to practically nothing. Death may be due to pressure on the abscess, to rupture and gangrene of the abscess-wall, to pneumothorax, to pneumonia, to associated dysentery, or to other intercurrent disease. Recovery may follow encystment or, possibly, absorption of the abscess.

Diagnosis.—Of all the grave tropical diseases, none is so frequently overlooked as abscess of the liver. Acute sthenic cases are readily enough recognized; not so insidious asthenic cases.

The most common mistakes in diagnosis are: (1) Failure to recognize the presence of disease of any description, even when an enormous abscess occupies the liver. (2) Misinterpretation of the significance and nature of a basal pneumonia—a condition often accompanying suppurative hepatitis. (3) Attributing the fever symptomatic of liver abscess to malaria. (4) Mistaking other diseases for abscess of the liver, and vice versa-for example, non-suppurative hepatitis, such as that attending subtertian malaria; suppurative hepatitis before the formation of abscess; syphilitic disease of the liver—softening gummata which are often attended with hectic fever; bronchogenic carcinoma; bronchiectasis; atypical pneumonia; tuberculosis; pylephlebitis; suppurating hydatid; suppurating actinomycosis; gall-stone and inflammation of the gall-bladder; subphrenic abscess due to ruptured gastric or duodenal ulcer, or appendix abscess; abscess of the abdominal or thoracic wall; pleurisy; encysted empyema; pyelitis of the right kidney; schistosomiasis; scurvy and similar blood-diseases associated with hepatic enlargement; ulcerative endocarditis; kala-azar; undulant fever; trypanosomiasis, tuberculosis, and malignant disease. Any of these may be attended with fever of a hectic type, increased area of hepatic percussion dullness, and pain in or about the liver.

Differential diagnosis from suppurative cholecystitis without the aid of a "shadowcol" examination may be particularly difficult.

Cantlie originally classified pus in the neighbourhood of the liver into :-

- (1) Suprahepatic abscess;
- (2) Intrahepatic abscess;
- (3) Infrahepatic or subhepatic abscess.

Suprahepatic abscess is not synonymous with "subdiaphragmatic abscess;" it means the formation of pus between the layers of the broad

ligament of the liver.

Frequently, a correct diagnosis can be reached only by repeated and careful study of the case in all its aspects. Golden rules in tropical practice are to think of hepatic abscess in all cases of progressive deterioration of health; and to suspect it in all obscure abdominal cases associated with evening rise of temperature, particularly if there be an upward enlargement of or pain in the liver, leucocytosis, and a history of dysentery—not necessarily recent.

Low-grade pneumonia of the right base in a tropical patient should always be regarded with suspicion, for it may indicate abscess of the

subjacent liver.

Perhaps the most common error is to regard the hectic fever of liver abscess as attributable to *malaria*. The regularity with which the daily fevers recur, the daily chilliness, or even rigor, coming on about the same hour, the profuse sweating, and other circumstances so compatible with a diagnosis of malaria, all contribute to this mistake. So common is the error that Osler declared he hardly ever met a case of liver abscess which had not been drenched with quinine. The periodicity of fever, and a polymorphonuclear leucocytosis should obviate so serious an error.

To mistake other forms of suppuration for liver abscess is not so serious, because in many suppurative diseases the treatment is the same as for liver abscess, and no bad result need follow if diagnosis is not quite accurate.

Intrahepatic suppuration may supervene in ascaris infestation, in melicidosis (p. 289), in ascending pylephlebitis secondary to appendix abscess, in diverticulitis and, rarely, in infections with hæmolytic Staphylococcus aureus, or very exceptionally with bacillary dysentery. Suppurating abscesses have been reported secondary to duodenal ulceration and enteric infections. Carcinomatosis of the liver, unaccompanied by jaundice, may simulate amæbic abscess. A right perinephritic abscess may have to be considered. In subdiaphragmatic abscess caused by perforation of a gastric or duodenal ulcer, an abdominal swelling can usually be recognized occupying a triangular area on the affected side. Gas is usually present and can be recognized by a resonance in the upper part which serves to distinguish it from liver abscess.

Pancreatic cyst elevating the left (less often the right) lobe of the liver may imitate an abscess, but it is not necessarily accompanied by fever. As a rule, it forms a definite tumour of considerable size in the left hypochondrium. Solitary non-parasitic cysts of the liver or polycystic disease

may also have to be considered. Phantom tumour may give rise to difficulty, but this gradually disappears under a general anæsthetic.

A serious error is to overlook the presence of leukæmia, kala-azar, pernicious anæmia or scurvy, and to proceed to aspirate an enlarged

liver on the supposition that the symptoms arise from abscess.

Amœbic abscess of the liver which has ruptured through the diaphragm may have to be differentiated from many other pulmonary conditions, such as broncho-pneumonia, tuberculosis, actinomycosis, and malignant disease of the lung.

The presence of Entamæba histolytica cysts in the fæces is suggestive but by no means conclusive, of amæbic abscess. They are usually found



Fig. 78.—Visualization of amobic liver abscess by puncture and injection of lipiodol in erect position. (After Snapper, "Chinese Lessons to Western Medicine.")

in about 45 per cent. of all cases. Occasionally the amœbæ may be cultured from the fæces in cases in which they are not detectable by the

microscope.

X-ray examination may confirm the upward enlargement of the liver, and bulging, "tenting" or blurring of the outline of the right dome of the diaphragm and shadowing of the right costophrenic angle indicating effusion. Screening usually shows that it does not move on respiration (Plate XIV). Paradoxical movement (rising with inspiration) is sometimes seen. Should, however, the abscess be situated in the centre of the liver, even if of considerable size, no definite information is usually obtainable by radiography except when the abscess has become partially encysted

In cases with cardiac or pulmonary embarrassment, aspiration can be efficiently carried out under local infiltration of skin and muscles with 2 per cent. novocain, to which is added 1 in 1000 adrenalin in the proportion of 10 drops to the ounce. The passage of the needle through the liver substance is painless. Should, however, the abscess point into the abdominal cavity, a general anæsthetic is advisable, for an open operation may become necessary. Occasionally the pus proves to be so thick that complete evacuation takes an hour or more; in these circumstances eusol in saline (half-strength) should be injected into the abscess cavity to dilute the pus.

An after course of combined emetine-bismuth-iodide and quinoxyl should be given to eradicate the amœbic infection from the bowel.

Open operations.—The indications for open operation are:—

(1) When after repeated aspiration no pus is obtained, but indications of its presence are too strong to be ignored.

(2) When an abscess points in the epigastrium, i.e., is situated

in the left lobe of the liver.

(3) When there is a large amount of pus which has been secondarily infected by bacteria and has not yielded to treatment by aspiration.

The route for opening the thoracic or abdominal wall varies according to circumstances as follows:—

Transperitoneal route.—When pus is struck below the costal margin, the aspirator needle is left in situ and the abdomen is incised for a length of 3 in. (Kocher's incision), the intestines being guarded with packing. If adhesions are present, a sinus forceps is directed along the needle and pushed through into the abscess, and the blades are opened after withdrawal of the needle. The finger should be inserted into the abscess cavity. When the first gush of pus ceases, the exit is lightly plugged with gauze, the margins of the liver wound are carefully sutured to those of the parietal peritoneum, and the remainder of the wound closed. The gauze plug is now removed, and a wide drainage-tube, provided with a flange and lateral openings, is introduced to the bottom of the abscess cavity. Some surgeons use a wide-bore drainage tube, such as Tudor-Edwards empyema tube drain, pushed right to the bottom of the cavity to prevent extravasation.

Transpleural route.—Should the abscess be struck through an intercostal space, a couple of inches of (the 8th and 9th) ribs had better be resected. The diaphragm should then be stitched to the thoracic wall, or better, to the skin as well, when the abscess may be opened with a forceps. An attempt should be made to stitch the capsule of the liver to the diaphragm. Should the pleura be opened, pneumothorax will result, but this is not necessarily serious. On no account should pus be permitted to enter the pleural cavity.

Sometimes it is simpler to expose the ribs and denude them of tissues. An iodine gauze pack should be inserted underneath the ribs and left for 3 to 4 days. Artificial adhesions are formed in the costophrenic sinus by a process of aseptic inflammation. Shears are then used to resect the ribs. Post-operative drainage is ensured by sinus forceps and a wide-bore tube. Dakin's solution may be used to irrigate as it exerts a solvent action on the liver abscess wall. The modern treatment of introducing penicillin solution into the abscess cavity through a ureteric catheter kept in situ has simplified the treatment of secondarily infected abscesses. The initial dose is 25,000 units to 51,000 units in the second week

at five-hourly intervals for 15 days (North and Hirschfield). Hurst recommended the instillation of 50,000 units every 48 hours with remarkable results.

Treatment after operation.—For the first two days after a liver abscess has been opened the discharge is considerable, and the dressing may have to be changed frequently. Very soon, however, should the case do well, the discharge rapidly diminishes, and the dressing requires renewal only every other day, or every three or four days. During the first week the drainage-tube, provided it be acting efficiently, should not be disturbed, more particularly as it may be difficult to replace. Later, it may be removed and cleaned, and, when discharge has practically ceased, cautiously shortened. It is a great mistake to begin shortening the tube before it is being pushed out, or so long as there is any appreciable discharge. If there is the slightest indication, such as rise of temperature, that pus is being retained, the drainage must be rectified and the sinus, if necessary, dilated with forceps and finger, and a full-sized drainage-tube introduced as far as it will go. If this does not suffice, a counter-opening may have to be made. Delay in remedying imperfect drainage is a serious—it may be fatal—error.

Should an abscess be found septic, or should it become so, it must be flushed out daily, or twice a day, with a weak non-mercurial antiseptic, and a counter-opening made if necessary. Continuous drainage by the Carrel-Dakin tube method and daily eusol irrigation are often very successful. Where there is a thick necrotic zone delimiting the abscess, this continuous irrigation is highly necessary, and in order to dissolve the thick pus the injection of a ferment—enzymol (Fairchild) in the strength of 1 drachm to the ounce of water—is

useful.

After a liver abscess has been opened and is draining well, temperature rapidly falls, and in a few days, or almost at once, becomes normal. Should fever persist, it is to be inferred either that the drainage is inefficient, or that there are more abscesses in the liver, or that there is some complication. If another abscess is suspected, it should be sought with the aspirator and, if found, drained.

It is advisable to give emetine in 1 gr. doses hypodermically, together with chloroquine, both before and after operation, and continue them for a fortnight, whichever operation is employed.

Treatment of abscess discharging through the lung.—If an abscess is discharging through the lung and, although emetine and chloroquine have been freely administered, is not progressing favourably, the question of more efficient drainage by surgical means must be considered. There are two possibilities which render interference desirable: (a) Continued discharge of pus and blood, with or without attendant hectic fever-a condition which, if it persist, will, in all probability, in the end, kill the patient. (b) Not infrequently, prolonged discharge through the lung may induce fibrotic changes, pneumonia, or abscess with all its attendant dangers, such as thrombosis or abscess of the brain. (Plate XVI.) In all cases of abscess discharging through the lung a careful register should be kept of three things-body-temperature, daily amount and character of expectoration, and, once a week, the weight. If temperature keeps up, if the amount of pus continues the same or increases, or if the patient continues to lose weight, an attempt should be made at all risks to reach and drain the abscess from the outside. If temperature remains normal, if pus gradually or intermittently decreases, and if the body-weight is maintained or increases, operation is unnecessary or at all events, should be deferred.

Modern medical treatment with full doses of emetine or chloroquine, maintained over a long period, generally exerts an almost miraculous effect and renders operative interference unnecessary.

In exploring the liver in such cases, it must be borne in mind that most likely the abscess cavity is collapsed, and that the sides of the abscess may be in contact. Such an abscess is not likely to be discovered unless the needle be thrust in to its full extent and, whilst a good vacuum is being maintained in the aspirator, slowly withdrawn. If by good fortune the abscess has been traversed, then, when the end of the needle is crossing the cavity, a small amount of pus will be seen to flow.

Treatment of abscess rupturing into a serous cavity.—When there is evidence that an abscess of the liver has ruptured into the peritoneum, into the pleura, or into the pericardium, the particular serous cavity involved must be opened and at once treated on general surgical principles; otherwise the patient will almost surely die. In the circumstances the surgeon will be justified in assuming great risks.

2. AMŒBIC ABSCESS OF THE BRAIN, SPLEEN, AND PERICARDIUM According to Armitage, 48 cases of amœbic abscess of the brain have been recorded, for the most part from Egypt. Like hepatic abscess, it is

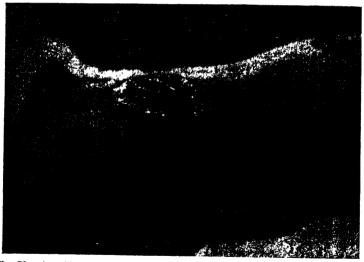


Fig. 79.—Amœbic granuloma and ulceration of abdominal parietes surrounding colostomy.

more common in men than in women. It is generally solitary, and may be regarded as a metastasis of hepatic abscess, though one unassociated with any other except an intestinal lesion has been described by Halpert and Ashley (1945). The mechanism by which amœbæ reach the brain is by no means clear. The pressure symptoms resemble those of a cerebral numour, and the abscess is invariably fatal. Amœbic abscess of the spleen

has been recorded by Maxwell, Rogers, Chatterji, and by the Editor. Authentic cases are extremely rare and not necessarily associated with liver abscess. In the case reported by the Editor there was considerable splenomegaly and amcebic cysts were absent from the fæces. On the other hand spontaneous splenic abscesses due to infarction or to thrombosis of the splenic artery are, according to Gelfand, quite common in African negroes. Amebic pericarditis, usually secondary to liver abscess, has been recorded.

3. AMŒBIC INFECTION OF THE SKIN, BONE AND SUBCUTANEOUS TISSUES

Since 1892, it has been known that the skin may be subject to amcebic invasion in the vicinity of a discharging liver-abscess sinus. Amcebæ have been demonstrated in sections of the skin, and they are susceptible to emetine. Gangrenous lesions of the abdominal wall and perineum have been described from time to time, especially by Engman and Meleney (1931), while Hu, in China, described a series of fourteen cases and showed that the condition is by no means rare. The Editor treated one such



Fig. 80.—Amœbic ulceration of skin. Ulceration of sacrum, coccyx and perineum. (W. B. Gabriel.)

case, in which the parietes in the vicinity of a colostomy and the abdominal wall were involved (Fig. 79), with discharge of feetid anchovy sauce pus. The patient was proved to have active amedic dysentery. Extensive gangrenous destruction of the buttocks and skin of the back was seen in St. Mark's Hospital, London, in an ex-soldier who had served in India fifteen years previously; though he had never suffered from clinical dysentery, E. histolytica cysts were present in the fæces. The lower part of the rectum, the pelvic floor and the perineal tissues had been destroyed. Response to emetine therapy was quite remarkable. (Fig. 80.) This condition was first described by Maxwell as fistulous disease of the buttocks in South China. McConaghey (1945) has published a similar case in a woman with a pararectal abscess spreading to the vagina and perineum.

Anabiasis cutis is a secondary infection of papillomata around the anus. The lesions have a punched-out appearance, and resemble in

this respect intestinal amœbic lesions (Hu).

Morton and Soutar (1947) have found active $E.\ histolytica$ in an abscess of the buttock secondarily infected with staphylococci in a carrier of $E.\ histolytica$ cysts. There were two ragged cavities communicating with one another. The amœbæ were found lying subcutaneously and there was no connection with the rectum. Norwich and Muskatt (1946) treated an amœbic ulcer of the buttock connected with a pararectal abscess in a negro with amœbic dysentery. Rose (1952) found an abscess in the middle third of the femur extending down to the bone. $E.\ histolytica$ were found in the pus and the lesion was cured by emetine.

4. GENITO-URINARY AMŒBIASIS

A number of uncritical papers have appeared describing as amœbæ large prostatic or other inflammatory cells which may be present in subacute cystitis or prostatitis, but occasionally vegetative forms of \$\overline{E}\$. histolytica are found in the urinary sediment, sometimes derived from a fistulous track between the ulcerated rectum and the bladder (Craig). Amœbic ulceration of the urethra in the male, as well as of the cervix uteri in the female, have been reported by \$Hu\$ in China, and amæbæ have been demonstrated in the tissues in microscopic sections; \$\overline{E}\$. histolytica in the urine may be derived from this source, but an amæbic abscess of the epididymis has been reported from China by Warthin. Murgatroyd has treated one extraordinary case where amæbæ were present in all specimens of urine passed, although no lesions of the bladder could be visualized by cystoscopy. The organisms were apparently derived from the vesiculæ seminales. This is all the more exceptional as Watson and others have shown that \$\overline{E}\$. histolytica cannot survive in urine. Rose (1946) has described amæbic vaginitis in China. There were inflammatory ædema of the vaginal wall with ragged ulcers.

5. PULMONARY AMŒBIASIS

This type of case is distinct from pulmonary abscess secondary to that of the liver where infection of the lung tissue results from direct extension of the hepatic abscess, or by rupture, into the bronchus.

In primary pulmonary amœbiasis the amœbæ reach the lung by direct embolism from the bowel. Having gained the pulmonary circulation, they form firm nodules, which later break down into small abscesses. The symptoms produced closely resemble those of a fugitive broncho-pneumonia, or some form of tuberculous infiltration.

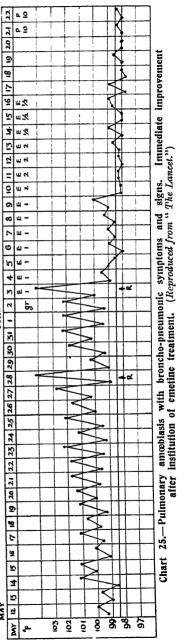
These patients, who have been at some time the subjects of amœbic

suffer from pulmonary with profuse purulent symptoms, expectoration, sometimes tinged with blood, and respiratory distress with intermittent pyrexia. They are apt. however, to have rigors, which may serve to differentiate the condition from other respiratory diseases. physical signs vary, but are usually those of broncho-pneumonic consolidation, detectable at the border of the scapula, especially on the right side. Skiagraphy may be of little avail in diagnosis. Amœbæ have not been recorded in the sputum. There is, as a distinct leucocytosis. response to emetine treatment is rapid and almost diagnostic (Chart 25). full course of injections should be given.

BALANTIDIAL DYSENTERY

The occasional occurrence of Balantidium coli in the fæces, particularly in association with dysenteric diarrhea, has been recognized for the last fifty years. It is only since Strong and Musgrave called attention to this subject that Balantidium coli has come to be regarded as the germ cause of a particular type of colitis resembling in many respects amœbic dysentery. The parasite has been studied from the zoological standpoint, more especially in temperate climates, but it seems probable that extended observations will show that it is, equally if not more prevalent, in warm climates. It is a common parasite of the pig, and produces a fatal form of dysentery in monkeys in captivity, especially chimpanzees. Human cases have been reported all over the world, but especially from Germany and France, in those who tend domestic pigs. It is thought that cysts are transferred from the hands to the mouth during the handling of the intestines of infected animals. Mackenzie and Bean (1938) recorded the first case in England in a mental patient, and a \$ second has been described.

How it attains the human intestine is



not known, but as it is a common parasite of the pig, these animals should be regarded as the usual source of infection. Balantidium may live for a considerable time in water or fæces (one hour to three days). In liquid stools it exhibits great activity, indulging in locomotive as well as in rotatory movements. Recently it has been cultivated on artificial media. For further description, see p. 934.

Geographical distribution.—Balantidiasis in man has been recorded from Russia, Scandinavia, Finland, Germany, France, Austria, Holland, Italy, Spain, Siberia, China (Tsingtau), Georgia, the Philippines, Cochin China, Andaman Islands, Hawaii, Mauritius and Rodriguez, Egypt, and the Sudan. Cases have also been reported from North America, North and South Carolina. McCarey (1952) reported a series of 87 cases from Abadan, S. Persia. There was no

connection with pigs.

Pathology.—There is little or nothing to distinguish the gross as well as the microscopic pathology from that of amœbic ulceration. The organisms have been found by Strong, Martini and Walker in the mesenteric glands. In thirty autopsies a variety of dysenteric lesions, from catarrhal congestion and diphtheritic patches to extensive ulceration, have been described. On section, Strong demonstrated the balantidium, not only in exudates on the surface of the bowel, but congregated in large numbers in the follicles, or embedded in the tissues forming the base of the ulcerations, including the submucosa, muscular coats, and even in the lumen of blood-vessels and lymphatics. The early lesions are minute hæmorrhages; later, ulceration and abscesses appear. Bowman stated that the colon throughout its whole extent may be a mass of ulcers from which hang shreds of necrotic tissue—lesions resembling those of amœbic dysentery.

Symptoms.—These are, in the present state of knowledge, indistinguishable from those of amœbic dysentery. The disease is chronic, its special nature being discoverable only on microscopic examination of the stools. Generally, only one or two balantidia are found, but as many as twenty may be seen in every field of the microscope. The blood usually shows no change: there is no leucocytosis and the polymorphonuclears represent 70 per cent. The ulcerations in the bowel, revealed by sigmoidoscopy, resemble those of intestinal amœbiasis as described by Mazza, Alvarado and Schürmann (1932). The mortality in 111 cases collected by Strong was 29 per cent.

Treatment.—Young and Burrow (1943) claimed to have cured seven cases with carbarsone, 0.25 grm. twice daily for 10 days. This should be repeated if there is relapse. Methylene blue enemata, 2 pints of a 1 per cent. solution, are claimed to give good results. Westphal praises Acranil—hydrochlorate of acridine. Shun-Shin (1947) claimed cures from intramuscular injections of $\frac{1}{4}$ gr. of biniodide of mercury and this has been confirmed by Pramanik. In vitro a 1: 100,000 solution killed the balantidia instantaneously and retention enemata in this strength were well tolerated. For children the dose by intramuscular route is $\frac{1}{24}$ gr. $\frac{1}{10}$ gr. and for the adult $\frac{1}{6}$ gr. McCarey recommends acetarsol, 4 gr. three times daily for 5 days, and Brummer tablets of 2-phthalylsulphanilaminothiazole; Weinstein and others give terramycin in divided doses over 10 days. The total is 17 grm.

III. HELMINTHIC DYSENTERIES

Schistosomal dysentery.—Adeno-papillomata or ulcerations of the large intestine evoked by passage of eggs through the intestinal wall, are found in Schistosoma mansoni, S. japonicum, and exceptionally in S. hæmatobium infestations. The dysentery thus produced is met in those countries in which the parasites occur.

The stools contain yellow or bile-stained mucus with clots or streaks of blood, in which the schistosome eggs can be found under a low power of the microscope. Eosinophilia associated with symptoms of dysentery is highly suggestive, and diagnosis should, if possible, be confirmed by the discovery of the characteristic eggs in the fæces. Sigmoidoscopic examination should help in doubtful cases. Pathologists should bear in mind that eggs are more easily found in the outer zone of solid fæces than in more central portions. Usually, pus cells in the fæces show a high proportion of eosinophils.

Infection with Œsophagostomum apiostomum and O. stephanostomum (pp. 975, 977).—These are rare intestinal parasites of man in Brazil, Northern Nigeria, Central Africa and Indonesia. When numerous they may give rise to dysenteric symptoms. The adult worms encyst under the submucosa, and may, together with their eggs, be recognized in the dysenteric discharges. Nodules in the execum and ascending colon have been described by Lie Kian Joe.

Infection with other helminthic parasites.—Chronic diarrhea and possibly dysenteric attacks have occasionally been noted in intestinal infections with Fasciolopsis buski (p. 937), Paragonimus ringeri (p. 942), Heterophyes heterophyes (p. 940), and Strongyloides stercoralis (p. 979).

DIFFERENTIAL DIAGNOSIS OF THE DYSENTERIES

Mixed infections of different forms of dysentery may, of course, occur in those countries in which these diseases are endemic.

Combined infections of amedic and bacillary dysentery are the most frequent. Such cases do not usually occur in temperate countries, but during the course of severe epidemics of bacillary dysentery, when bacillary infection may be grafted upon some long-standing amedic ulceration of the bowel. On the other hand, this dysentery may be followed by amedic invasion of the bowel, which renders diagnosis still more difficult.

Bacillary dysentery occurs quite commonly as a terminal event in intestinal schistosomiasis, and amœbic ulcers may sometimes be associated with the same condition.

Giardiasis.¹—Of the intestinal flagellates which appear in the fæces, perhaps Giardia (Lamblia) intestinalis has the best claim to be regarded as pathogenic. The usual habitat of the parasite is in the upper part of the small intestine, but it may also heavily infest the duodenum. When newly passed in the fæces it is very active, presenting a characteristic appearance. During the passive stages cysts appear in the fæces in enormous numbers, and may be found associated with those of E. histolytica. Giardia cysts are generally found in 4-16 per cent. of normal natives of the tropics. Other species are found in mammals and in reptiles, and one in the mouse, Giardia muris, is closely allied to the human parasite. In children in Northern countries giardia infection is three times as common as in adults. (In America 48·1 per cent. of industrial school children.) For a description of G. intestinalis, see p. 932.

¹ Giardiasis or lambliasis is mentioned in this section for the sake of completeness, although the diarrhoea associated with the parasite cannot strictly be classified as a dysentery.

In England and in Canada the parasite has been found in the intestine of quite a large number of normal children, while Boyd, Silverman, and others have shown that it can occasionally be demonstrated in the duodenal juice, bile, and gastric contents.

Some regard this parasite as pathogenic on the grounds that it is found in large numbers when the stools are liquid, and that quantities of mucus are passed containing active parasites.

Giardia infection is associated at times with a type of recurring diarrhea accompanied by abdominal discomfort. The stools may be of a peculiar clay colour and pultaceous consistence, and may resemble those of tropical sprue, or in English children, those of cœliac disease (R. Miller, 1926). Fat absorption has been found defective and excretion of bile below normal; both are attributed to mechanical effects of these parasites on the intestine. After these attacks, the encysted forms of G. intestinalis are present in large numbers in the fæces. Relapses tend to occur periodically, but eventually tolerance is acquired. Flatulence is almost invariable. In the acute stage the abdomen is tender and there is general discomfort. Veghelyi, who made observations on children in Budapest. described anorexia, headaches, dizziness, abdominal pains, and anæmia. attack is not accompanied by emaciation, and symptoms probably originate from mechanical irritation, not from destruction of the mucosa, though in mice, in which similar parasites cause diarrhea, they may penetrate the submucosa. Giardia infections are intractable and may persist for years. Hegner thought that the number of these parasites is dependent upon the diet as they tend to disappear from the fæces when the patient is fed on a protein dietary.

Treatment.—It is difficult to be certain of complete extirpation of these protozoa, for giardia frequently reappear in numbers in the fæces after an absence of several months. Apparently the parasite itself is subject to periods of great activity followed by periods of quiescence.

Atebrin (mepacrine, quinacrine) is specific, both for the active phases of the parasite and for the cysts. This claim, originally put forward by L. Brumpt, has been abundantly confirmed from many sources. The parasites disappear from the fæces after a course of 0·1 grm. three times daily for 5–7 days, in adults; though in children two tablets daily suffice. Sometimes it may prove necessary to repeat the course. Probably giardia is mildly pathogenic, because associated symptoms also disappear after treatment. German and Scandinavian authorities prefer Acranil, the hydrochlorate of an acridine compound, in doses varying from 0·25 grm. daily for children under two, to 1·5 grm. daily for 5 days in those over ten. This drug is said to be more easily tolerated than atebrin.

Nivaquine 0.3 grm. daily is recommended by Carri and Shisani (1950).

OTHER FORMS OF DIARRHŒA AND DYSENTERY ASSOCIATED WITH INTESTINAL PARASITES

The common intestinal flagellates, Trichomonas intestinalis and Chilomastix mesnili (see pp. 931, 930), though occurring commonly in diarrhœic and dysenteric stools, have little claim to pathogenicity. They are frequently present in large numbers in the fluid fæces of patients convalescing from bacillary or amoebic dysenteries. Probably the presence of large numbers of these flagellates in the bowel contents is due, to a great extent, to the fluid medium in which they flourish; but when a case of chronic diarrhœa is encountered and no other obvious signs can be found, and where large numbers of active flagellates are lashing

about in liquid fæces, it becomes difficult not to assign some pathogenic properties to these apparent agents of disease. Hence the term Flagellate Dysentery has arisen—a term which probably indicates that the host has been exposed to abnormal intestinal infection. These organisms usually disappear after vigorous lavage of the bowel by irrigations of 2 per cent. sodium bicarbonate combined with stovarsol (gr. 4), or spirocid, in similar dose—two tablets daily for eight to ten days.

Spirochætal dysentery is attributed to the presence of numbers of spirochætes in the intestinal canal. These organisms, composed of three or more simple spirals, are known as *Spirochæta eurygyrata*, but they are not usually regarded as pathogenic.

Intestinal coccidiosis has to be considered, especially *Isospora hominis* (see p. 933), which causes diarrhea, with mucus and Charcot-Leyden crystals in the fæces. Cases of this infection have been reported from all over the world, especially from the Near East and Indonesia.

Malarial dysentery.—A blood-stained discharge or, more frequently, hæmorrhage, may occur in the abdominal forms of subtertian malaria. The blood passed is very dark, due to petechial hæmorrhages from the intestinal mucosa. These are, as a rule, very serious cases. Instances were recorded by the Editor, in which malaria was first suspected from discovery of the subtertian parasite within the red blood-corpuscles present in the fæces. Besides the hæmorrhagic fæces, malaria should be suggested by the clinical aspect of the patient, sweating, icteric tint of sclerotics and skin and enlarged spleen. Violent diarrhæa may at times be the one outstanding clinical sign of an intensive subtertian infection.

Kala-azar dysentery.—Blood and mucus may be passed in the fæces in advanced cases of this disease, which may be due to an ulceration of the bowel by Leishman-Donovan bodies. The parasites are present in large numbers in the villi of the small intestine, and may form polypoid masses in the mucous membrane of the large intestine, whence they escape into the fæces.

Other conditions which may resemble dysentery.—There are other perhaps more familiar conditions, not necessarily of tropical origin, in which dysenteric symptoms may occur

Of all common diseases with which mild dysentery may be confused, the first place must be given to internal hæmorrhoids. A correct diagnosis is readily made. Again, profuse offensive diarrheic motions with blood and mucus may be passed in tuberculous ulceration of the large bowel, which may be comparatively common in the tropics. Colitis, ulcerative, membranous, or hæmorrhagic, resembles bacillary and amoebic dysenteries in clinical features and in the character of the stools, but can be differentiated by microscopic examination of the fæces, as well as by sigmoidoscopy. Idiopathic ulcerative colitis (colitis gravis) is becoming increasingly common and has to be differentiated from the bacillary dysenteries. It is undoubtedly a disease sui generis and is distinguished by pyrexia, toxæmia, intense anæmia, a tendency to spontaneous cure, and great liability to relapse. A very acute form sometimes follows cystoscopy. or instrumental investigation of the genito-urinary tract, and has been shown to be due to mercury poisoning from instruments sterilized with mercuric evanide. Mucous colitis, or the syndrome which is commonly known by that name, is a frequent sequel of both bacillary and amoebic dysentery and is frequently confused with both. Stercoral ulceration, produced by chronic constipation associated with myxœdema, may give rise to a blood and mucous discharge. Certain surgical conditions—simple polypus, malignant disease, intussusception, even syphilitic disease of the rectum, or rectal stricture in lymphogranuloma inguinale (p. 649)—the diagnosis of which should be determined by digital examination—must be kept in mind. *Polyposis* is a very distressing condition which usually undergoes malignant degeneration. Foreign body in the rectum is another possible diagnosis.

Blood and mucus are often passed in diverticulitis, which is quite common in tropical practice. In paratyphoid B. infections ulceration of the large intestine may give rise to blood and mucus in the stools. Food poisoning due to organisms of the Salmonella group may sometimes cause confusion by producing somewhat

similar symptoms.

CHAPTER XXXIII

TROPICAL SPRUE AND HILL DIARRHŒA

Synonyms.—Tropical Diarrhœa; Aphthæ Tropicæ; Psilosis; Ceylon Sore Mouth.

Definition.—A peculiar and dangerous form of chronic disturbance of function of the whole or part of the mucous membrane of the alimentary canal. Although essentially a disease of warm climates, tropical sprue may develop for the first time in temperate countries in individuals who have previously resided in the tropics or subtropics.

Geographical Distribution.—(Map VI)—South China, Philippines, Cochin China, Japan, Java, the Straits Settlements, Ceylon, India, Mauritius, a few cases from Fiji, more frequently in the West Indies, the Southern United States, Porto Rico, Central America, the Guianas, and Queensland. Isolated cases have been recorded from Iraq, Egypt, Palestine, North Africa and Russian Turkestan. In Central, West and East Africa it is problematical whether tropical sprue does occur, though Luckoff (1943) described it in natives of the Orange Free State, and Gelfand claims to have seen a sprue-like disease in Europeans in Rhodesia. During the 1939–1945 war cases in British soldiers have been seen from the Mediterranean—Malta, Southern Italy and Gibraltar.

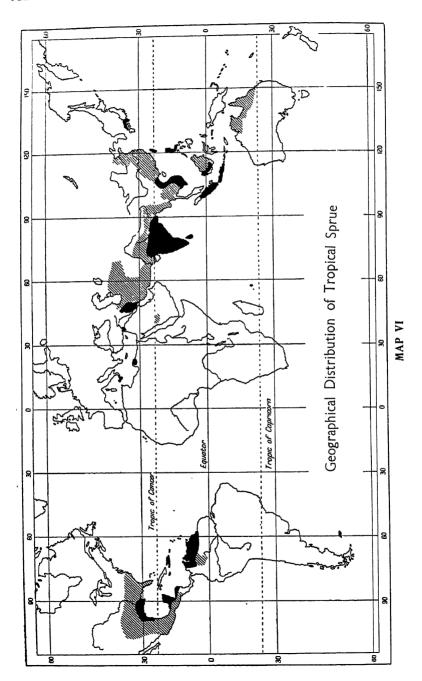
Epidemiology and endemiology—Information so far on this subject suggests that sprue is a regional, as opposed to a climatic, disease and it pre-eminently affects Europeans. There was formerly doubt of its existence in native races. Highly pigmented races, usually the indigenous inhabitants of the endemic country, are less liable than immigrants, though sprue was prevalent in Indian troops in Burma in 1944-45.

The disease is apt to occur in one or more members of the same family. Many instances of sprue in husband and wife have been recorded, probably from exposure to the same influences. During the Burma campaign, 1943–45, sprue occurred in epidemic form in British troops (see below). Atmospheric temperature per se has no influence, for sprue originates at high altitudes in Ceylon and in the Himalayas, where the climate approximates to that of Europe.

There are residences in Bombay and bungalows in Ceylon which are notorious for the incidence of sprue in successive tenants; these have been known as "sprue houses" and have given rise to a popular theory that the disease is connected in some way with "dry-rot" in wooden beams.

As a rule, sprue attacks those of middle age or over. Children are rarely affected, though there is one authentic record in an English boy from Ceylon of eleven years of age (Miller). Amongst Europeans both sexes appear equally liable.

Ætiology.—A nutritional deficiency, as originally postulated by McCarrison, Elders and Nicholls, at one time appeared to be the most



likely factor. Discoveries on the ætiology of pellagra and the fact that in fully developed tropical sprue there are signs and symptoms which may be ascribed to vitamin deficiency, mainly of the vitamin B₂ complex, have tended to fortify this theory. But tropical sprue is undoubtedly a disease sui generis with clinical characteristics so typical as to admit no other assumption (see below). However, Ayrey (1948), as the result of extensive experiences in the jungles of Burma in troops existing on K rations, has revived the theory of malnutrition due to deficiency of vitamins of the B₂ complex.

Biochemical studies, by Fairley and others, suggested that the phenomena of tropical sprue can best be explained in terms of a metabolic breakdown of the gastro-intestinal tract, characterized by defective absorption in the small intestine, primarily connected with defective secretion of Castle's intrinsic factor by the pyloric or Brünner's glands. The well accepted fact that the anæmia of sprue resembles that of pernicious anæmia, and responds in like manner to the extrinsic factor (in liver extracts), was regarded as suggestive. Then the glossitis appears to bear the same significance as in pellagra, pernicious anæmia and idiopathic steatorrhœa, in all of which it apparently represents the outward expression of B_2 avitaminosis.

Furthermore, as in pellagra, there is a pre-sprue, or larval condition, of which glossitis is the outstanding sign, which may be indistinguishable from a similar stage in larval pellagra. A connecting link between sprue and pellagra is also suggested by the fact that pellagrous symptoms may sometimes be engrafted on sprue as a secondary phenomenon.

It was suggested by Bennett, with cogent arguments, that the sprue syndrome may be regarded as the expression of "chronic jejuno-ileal insufficiency" of which the outstanding signs are steatorrhæa, emaciation, meteorism, glossitis and megalocytic anæmia; and that these phenomena may be evoked by a number of conditions. The main argument for this view lies in the results of gastrojejuno-colic fistula, which reproduce the main signs and symptoms of sprue, whilst these sprue-like signs and symptoms disappear when the defect is remedied by operation. Sprue symptoms may also supervene on resection of four feet, or more, of the lower ileum (Markoff), or may be produced by interference with chyle absorption in lymphadenomatous infiltration of the mesenteric glands, or by gross ulceration of the ileum.

Other diseases closely simulate tropical sprue, such as cæliac disease in children and idiopathic steatorrhæa in adults. These are probably the outcome of other forms of malabsorption from the small intestine, whilst the latter has been shown by Frazer to be caused in some manner by the gluten of wheat. In idiopathic steatorrhæa the syndrome possibly represents an exaggerated phase of tropical sprue with implication of factors other than the vitamins of the B₂ complex. It is conceivable that the full syndrome is produced, not so much by the absence of essential vitamins from the dietary, as by failure to absorb them, or by lack of biosynthesis in the bowel owing to abnormal bacterial flora. This suggestion has received support from a paper by A. C. Frazer (1949). The selective nature of the vitamin-B deficiencies—nicotinic acid, riboflavin, pyridoxin and folic acid—is striking. All these are essential growth factors for bacteria, especially those known to be present in the upper part of the small intestine in sprue. These bacteria absorb the available vitamins causing deprivation of these factors in the host.

Obscure as the true ætiology of tropical sprue appeared to be before 1939 it must be confessed that the outcome of the most diverse and detailed investiga. tions which have been carried out by special teams of observers from 1942-45 in India and Burma have rendered the problem still more difficult of clarification. There, as is abundantly clear from the writings of Leishman, Keele and Bound. Black and Fourman and many others, tropical sprue in British troops behaved as an epidemic disease with an incubation period and a seasonal incidence. There were many opportunities for observation because sprue appeared on an unprecedented scale in many widely separated areas, quite unconnected with dietetic or climatic factors. It had a distinct regional distribution. For instance, though so prevalent in India and Burma, it was practically absent from the far greater numbers of combatants, American, British and Australian in the Pacific combat zones. These cogent facts appear to offer no other argument than that in its initial stages tropical sprue may behave as an infectious disease due to some undiscovered virus and that only in its later stages do the signs and symptoms of an avitaminosis become apparent. Leishman relates that in 1944 some 675 British troops had to be invalided to England on account of severe sprue. Whilst amongst Indian troops a similar malady appeared on a big scale and was termed (quite unnecessarily) "para-sprue" (Napier, Chaudhuri, Ayrey). Contrary to previous experience the length of stay in the tropics proved scarcely a factor. Three-quarters of the cases had less than two years' service. Some developed sprue within two weeks of arrival and one was taken off a transport on arrival in India with the fully developed sprue syndrome.

In East India the sprue season lasted from March to September with a peak incidence in June, but in areas of lesser incidence the season was less restricted. These months corresponded to the fly season and coincided with an outbreak of bacillary dysentery, but it was not a sequel to this disease. For instance, a previous dysenteric infection was obtained only in 9 per cent. In 1943 in Chittagong 50 per cent. of one unit developed the disease within three weeks of arrival. As regards the geographical distribution 65 per cent. of cases originated in Bengal, Assam and Burma; 15 per cent. came from West India; 13 per cent. from South India and Ceylon, and 5 per cent. from North India. At least one-third were in soldiers living under good conditions on full rations and often in an innocuous climate. In more than half the cases the full sprue syndrome was established within two months of onset of diarrhoea.

For the better appreciation of this very difficult subject it must be stated that authorities are by no means clear regarding the separation of "tropical sprue" from the allied syndrome—known, perhaps fallaciously, as "non-tropical sprue," a term introduced by Thaysen in 1932. Most of these severe and incurable cases are undoubtedly examples of what is known in England as idiopathic steatorrhæa, which in the opinion of the best-informed is quite a distinct and separable disease, though in some of its minor manifestations it must be confessed that differentiation becomes extremely difficult. Sprue-like symptoms occur in numerous other diseases and may make an evanescent appearance in the convalescent stages of bacillary dysentery, in mesenteric tuberculosis, gastrocolic fistula and diseases of the mesenteric glands.

Up to 1939 it was thought that vitamins of the B₂ complex were necessary for the absorption of fat by the villi of the small intestine. Stannus sought to explain the process as follows:—

The absorption of neutral fat in tropical sprue is normal, but that of fatty acid, glycerol, cholesterin and glucose defective, due to failure of phosphorylation. Calcium is deficient because it forms insoluble soaps with free fatty acids, and similarly there is deficiency of phosphorus. Other clinical phenomena were to be explained on similar biochemical grounds. The physiological lesion in sprue

was held to be failure of phosphorylation due to the defects of the enzyme system, the coenzymes of which are members of the vitamin B₂ complex.

These conceptions have been refuted by the important work on fat absorption by Frazer. Fat is mainly ingested as triglyceride in emulsion in particles less than 0.5 cm. in the lumen of the small intestine. The emulsifying system is dependent on a triple combination—fatty acid-bile salt-monoglyceride.

The intestinal contents of all varieties of fat-absorption have shown normal dispersion of fat and normal enzyme activity, but in a small number of cases of tropical sprue a peculiar flocculation of the intestinal contents has been observed.

Intracellular phase of fat absorption.—Fatty acids pass into the intestinal cells mainly in the form of soaps. Long-chain triglycerides are finely divided into particles as already described. The outer membrane of the intestinal cell has been shown to consist of fine canals and this fact supports the conception that particles do pass through the outer membrane in this particulate form, and it appears probable that the postabsorptive lipæmia is normally dependent on this process. By correlating chylomicrographs of serial blood-fat estimations it is possible to determine whether this absorption is normal. In the absence of lymphatic obstruction 60-70 per cent. of ingested fat without subsequent lipæmia suggests interference with fat absorption and is observed in tropical sprue, idiopathic steatorrhœa and gastro-colic fistula. Adrenalectomy does not affect absorption of fatty acids or tributyrin, but causes partial interference with absorption of long chain tryglycerides, but this returns to normal with adequate salt therapy. Thus the action of the adrenal cortex on fat absorption is mainly due to its effect on water and electrolyte metabolism and this has been shown to take place in severe cases of tropical sprue with dehydration (Black, 1946). It was originally suggested by Verzár and McDougall (1936) that adrenal deficiency constituted an ætiological factor in the sprue syndrome, but the results of cortene therapy do not support this hypothesis.

Alteration in composition and distribution of fatty material within the intestinal cell.—Resynthesis of triglyceride can be demonstrated in vivo, but it can be shown that phospholipid is formed within the cell during fat absorption so that it is probable that one important function of phosphorylation is to provide phospholipid for the change in interfacial film structure which occurs if the particles are to remain in a dispersed state in the protein environment of the blood stream.

The passage of fatty material through the finer membrane of the cell.—As the dosage of fat is increased it accumulates within the cells and it would seem that the addition of choline to the fat facilitates its passage through the inner membrane of the cell. Probably the phospholipid formed within the intestinal cell during fat absorption is lecithin, but probably other phosphatides may be involved. It may be concluded that vitamin deficiencies, possibly excluding choline, are probably not concerned with the ætiology of the fat absorption defect in the sprue syndrome.

Distributive phase of fat absorption.—Fatty acids mainly pass up the portal vein to the liver, while triglycerides take the lymphatic route and pass by the thoracic duct into the systemic circulation. The proportion of fatty material which passes by these two alternative routes might be varied without any great change in the quantity of fat absorbed. In the majority of cases of defective fat absorption there is no evidence of obstruction in the lymphatic pathway and alteration in the distribution of fatty material must be dependent upon changes in the lumen or cells of the intestine.

¹ A chylomicrograph consists of counting the fat particles in the bloodstream after fat absorption under the dark-ground illumination.

It is known that changes in the intestinal environment occur in a number of cases of defective fat absorption, but whether primary or secondary, or whether significant or not, has not been established, but as fat can be absorbed by two distinct mechanisms, each of which uses a different pathway, the proportion of fat which is absorbed in particulate form may be reduced with a corresponding increase in fatty acid absorption. The main factors concerned in changes in the distributive phase, apart from obstruction to the lymphatic pathway, are the pH in the intestinal lumen and the composition of the dietary triglyceride.

Frazer and his colleagues have shown that, though malabsorption of fat is the most conspicuous feature in tropical sprue, yet other elements of the diet are equally implicated. Recent published work by Frazer and his co-workers appears to have important bearings upon the etiology of steatorrhœa. The gastro-intestinal functions were investigated in children with cœliac disease

(1952).

Removal of wheat flour from the diet resulted in rapid improvement, both clinically and biochemically. Deterioration followed reintroduction into the diet of wheat flour or wheat gluten, but wheat starch had no harmful effect. The precise manner in which the gluten fraction disturbs gastro-intestinal function is being investigated. The agenization of wheat flour plays no part. When gluten is excluded, even in the early stages of treatment, there appears to be no need of restricting carbohydrates or even fat.

Pathology.—The heart has usually undergone "brown atrophy." The liver is atrophied, sometimes with fatty changes, and all the muscles and viscera are anæmic and wasted. With these exceptions and certain changes in the alimentary tract, so far as is known, there are no special lesions invariably associated with this disease. Occasionally, the pancreas shows fatty or granular degeneration of the cells, with softening of isolated acini and slight inflammatory infiltration of the connective tissue. These, however, are not more constant than are similar changes occasionally found in the liver and kidneys. Sections of the tongue show desquamation of the epithelium, especially from the surface

of the fungiform papillæ. Lesions of the alimentary tract.—In longstanding cases there is usually atrophy of the small bowel so as to render it almost diaphanous. Ulceration and erosion of the ileum leading to perforation and peritonitis have been described by the Editor, but these, as well as the destruction of the intestinal villi, are now thought by some to be secondary changes (Mackie and Fairley, and, more recently, Thaysen). The chief lesions are thinning and atrophy of the mucous membrane of the absorptive and secretory epithelium with some shrinkage of the villi. The changes are essentially those of degeneration and aplasia, but there are evidences of blood destruction in the mucosa, suggesting absorption of some hæmolytic substance in the intestines and destruction of blood in situ. In autopsies, where death has been sudden, it is surprising indeed what few naked-eye changes can be seen. Pathological changes are seen in the red marrow of the femur and the tibia. This is usually reduced in quantity, though there may be hyperplasia, as in pernicious anæmia. It is suggested that in sprue there is a toxin which primarily stimulates, but eventually exhausts the hæmopoietic system. Ulceration of the ileum, leading to perforation and general peritonitis, may be the cause of death.

The mesenteric glands may be enlarged, pigmented and fibrotic. The inflammatory changes in the mucosa and the invasion by round and plasma cells, formerly considered characteristic, are now held to be inconstant in appearance and extent, and possibly to be caused by the irritability brought about by acid fæces. As originally shown by the Editor in Ceylon secondary infection of the intestinal tract with the thrush fungus, Candida albicans, is not an infrequent

terminal event. There is an over secretion of mucus throughout the intestinal tract, more especially in the small intestine where this fungus grows.

Clinical pathology.—The stools of sprue are characterized by their light colour and excessive size; they may be five or six times the normal amount. Analysis reveals the ordinary elements of bile, notwithstanding the lack of colour. The excess of fat in the stools and low fat content of the blood (412.8 mgm. per cent.) indicate that a proportion is due to actual excretion of fat through the intestinal mucosa. (The normal is 600 mgm. per cent.). Normally, neutral fats in the fæces are to fatty acids in the proportion of 1 to 2; in pancreatic disease this ratio is reversed, and may be as high as 15 to 1; while in sprue stools more splitting of fats takes place, the proportion of neutral fats to fatty acids being as 1 to 3 or even 1 to 5. It is estimated that not uncommonly 50 grm. of fat is excreted in a single stool when the patient is existing on a mixed dietary. The average results of fat analysis of fæces is as follows:—

Total fat 60 per cent. Combined fatty acids 14 ,, ,, Free fatty acids ... 37 ,, ,, Unsoaped fat ... 45 ,, ,, Neutral fat ... 7 ,, ,,

High fæcal fat above 50 per cent. does not denote clinical severity (Keele and Bound). Many observers have insisted that in early cases there is no actual steatorrhœa. Samples of stools taken at different intervals vary very much in their fat content. It is necessary to collect all the specimens passed in twenty-four hours. Others insist that an average analysis should be made from stools collected over a period of five days. The fat intake for a period of at least three days should be known. Pallor of fæces may be due to alteration of the colour of the bile pigment (leucourobilin) and not necessarily due to fat.

Howell (1947) finds that in early cases, whilst the total fæcal fat is often within normal limits there is a significant rise in the split: unsplit fat ratio.

Black and colleagues (1947) found that no sprue patient has a fat absorption rate higher than 85 per cent. which is well below the normal value of 90 per cent., in spite of this there is considerable overlap in blood-fat curves in sprue and normals, so that in early sprue the chylomicron count is normal. In the most severe cases just over half ingested fat is absorbed and a fat absorption of 60 per cent. implies four times the normal amount of fat in the fæces. In untreated sprue fat absorption ranges from 51 to 85 per cent., but a rapid improvement in absorption follows liver injections.

The trypsin and other enzyme activities in the stools are normal. These figures indicate that in sprue pancreatic digestion proceeds quite normally, but that the products of digestion are not absorbed, probably because the contents are hurried through the small intestine. Malabsorption of fats may possibly be due to the same cause.

The blood picture of the fully-developed tropical sprue case is a megalocytic anæmia, the size of the cells varying from $7.8-8\,\mu$. The very variable degrees of anæmia coincide with the megaloblastic arrest in the bone

marrow, as seen by sternal puncture, but this is definitely less than that found in pernicious anæmia. In severe cases the marrow picture may be definitely hypoplastic. As a general rule, this grave anæmia occurs in patients over fifty years of age. In no instance, in the cases investigated, has the colour index been less than 0.7, but in the majority it is above that figure. In uncomplicated sprue the leucocyte counts are either normal, or there is a leucopenia associated with a relative lymphocytosis. Blood crises commonly occur and are characterized by a rapid and critical fall in the hæmoglobin and red blood-corpuscles. Usually associated with severe diarrhæa, it progresses to a fatal issue, without remissions and without those evidences of blood regeneration which are so typical of similar crises in pernicious anæmia. Hyperbilirubinæmia is found more frequently in malaria and in pernicious anæmia than in tropical sprue (Van den Bergh test).

The Price-Jones curve resembles that of pernicious anæmia, being characterized by marked asymmetry, broadening of the base, displacement to the right, and a definite increase of the diameter of the corpuscles to $8.07~\mu$. It therefore seems that deficient blood-production rather than excessive blood-loss constitutes the basis of sprue anæmia.

Serum-calcium and phosphorus content.—Fairley, Mackie and others have confirmed Scott's observations that the ionic calcium is lowered in sprue, 7.4-9 mgm. per 100 ml. of serum being constantly registered.

Blood cholesterol.—There is a definite hypocholesterolæmia, and Fairley has shown that the serum cholesterol averages 72.8 mgm. per 100 ml., the lowest reading being about 40 mgm. The cholesterol content rises rapidly with liver-

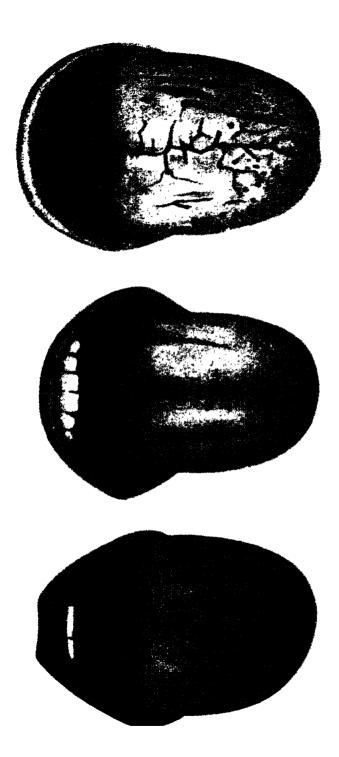
extract therapy and high-protein dietary.

Blood-sugar regulation.—Thaysen originally pointed out that in sprue, as well as in idiopathic steatorrheea and coeliac disease, there is an abnormally low blood-sugar curve, which is not due to impairment of glucose absorption, or to its destruction in the intestines. On the other hand Maegraith and colleagues (1946) have shown that the fructose curve under similar conditions is normal. Fructose is absorbed by simple diffusion.

The urine is highly coloured, especially in cases with pronounced anæmia. This is due to the appearance of urobilinogen and urobilin in pathological amounts, derived from the products of blood destruction, as it is estimated that in sprue anæmia the blood-cells are being destroyed nearly five times more rapidly than normal. The diastatic reaction has been investigated and has been found to be well within the normal limits. This method affords a means by which sprue may be differentiated from chronic pancreatitis. In acute sprue there is porphyrinuria, as in pellagra.

Gastric secretion.—In most cases there is a relative hypochlorhydria or a normal acid curve, but occasionally hyperchlorhydria may be present. In cases with severe anæmia there is usually achylia gastrica, but the gastric elements differ from those of pernicious anæmia in that acidity in sprue returns to normal after adequate treatment with liver extract and restoration to health.

Salt deficiency occurs in patients with low blood pressure, asthenia and signs of peripheral circulatory failure. These have low serum sodium and serum chloride levels. The plasma volume is low in relation to body weight. There is an abnormal loss of sodium, and to a less extent of chloride when the patient is put on a high intake of salt. Sodium and chloride are both retained and the serum chlorides rise to pormal. The blood pressure rises and clinical signs of



(P. Manson-Bahi)

PREPELLAGROUS AND SPRUE TONGUES

PLATE XVII

Chronic sprue tongue.

Acute stage of sprue with typical aphtha.

Avitaminosis (B2) tongue (prepellagrous), showing angular stomatitis.

dehydration disappear, whilst fat loss in stools is unaffected. The loss of electrolytes in the copious watery stools is the main cause of salt deficiency (Black).

Symptoms. Variability.—There is infinite variety in the combination and in the severity of the various symptoms of sprue, as well as in the rate of progress of the disease. In some instances it may be almost a subacute process, running its course in a year or two; in others, again, it may drag on intermittently for ten or fifteen years. Much depends on the circumstances, the character, the care, the treatment, the age and the intelligence of the patient.

General symptoms in a typical case.—In an ordinary fully developed case the patient—who is generally dark or muddy in complexion and much emaciated—complains of three principal symptoms: soreness of the mouth, dyspeptic distension of the abdomen, and looseness of the bowels—the last being particularly urgent during the early morning and part of the forenoon. He may also complain of feeling physically weak, of loss of memory, and of inability to take exercise or to apply his mind. His friends will probably volunteer the information that he is irritable and unreasonable. In addition to patchy pigmentation and general discolouration of the skin, dryness with depilation is common, as is also scaling of the parakeratotic type. This follicular hyperkeratosis responds quickly to treatment.

Mouth lesions.—The soreness depends on a variety of lesions of the mucous membrane, which, though painful, seem to be very superficial and vary considerably in intensity from day to day. During an exacerbation the tongue looks red and angry; superficial erosions, patches of congestion. and perhaps minute vesicles appear on its surface, particularly about the edges and tip. Sometimes, from the folding consequent on swelling of the mucous membrane, its sides have the appearance of being fissured. The filiform papillæ cannot be made out, although here and there the fungiform stand out, pink and swollen (Plate XVII). If the patient be made to turn up the tip of the tongue, red patches of superficial erosion, sometimes covered with an aphthous-looking pellicle, may very likely be seen on either side of the frænum. These aphthæ probably form beneath the epithelium and subsequently burst. On eversion of the lips, similar patches and erosions are visible; and, if the cheek be separated from the teeth, they may be seen on the buccal mucous membrane. Occasionally the palate is similarly affected; very often, also, the mucous follicles are enlarged, shotty, and prominent. The gullet and uvula may also be congested and, in places, raw and sore. "Cheilosis," or tissue paper-like changes on the lips, and angular stomatitis are seen in about 20 per cent. of cases in acute sprue.

In consequence of the irritation caused by these superficial and exceedingly sensitive lesions, the mouth tends to fill with a watery saliva, which may dribble from the corners. If the patient attempts to take any acrid food, strong wine, or anything except the very blandest diet, the pain and burning in the mouth are intolerable; so much so that, although perhaps ravenously hungry, he shirks eating. Not infrequently, swallowing is accompanied and followed by a feeling of soreness and burning under the sternum, suggesting that the gullet, like the tongue, is also irritated, raw and tender. During exacerbations the condition of the mouth becomes

greatly aggravated. Although during the temporary and occasional improve. ments it is much less painful, even then salt, spices, strong wines and all kinds of sapid foods sting unpleasantly; and the tongue, particularly along its centre, is seen to be bare and polished as if brushed over with a coating of varnish. At all times the tongue is abnormally clean and devoid of fur: during the exacerbations it is red and swollen; but during the remissions and when not inflamed, it is small and pointed, and, owing to the anæmic condition of the patient, it may be yellowish. The sore tongue and mouth may at first be the only signs, and they may persist for months or, it may be, for a year before complete sprue unfolds itself. The fiery red appearance of the tongue differentiates it from the "magenta tongue" of ariboflavinosis. Keele and Bound remark that the latter was never observed in sprue cases in Burma.

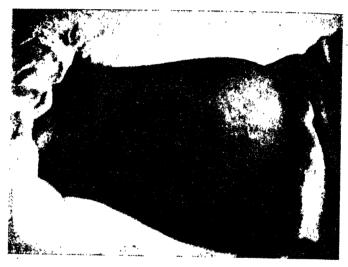


Fig. 81.—Sprue abdomen, showing intense meteorism.

The tongue may be regarded as a mirror of the gastro-intestinal tract so that probably similar changes (hyperæmia and inflammation) are present in the stomach and small and large intestines; thus the mucosa of the

rectum is inflamed, as can be demonstrated by sigmoidoscopy.

Dyspepsia.—Dyspepsia is usually very troublesome, the feelings of weight, oppression, and gaseous distension after eating being sometimes excessive. Very likely the abdomen swells out like a drum, and unpleasant borborygmi roll through the bowel (Fig. 81). Occasionally, though not often, there may be vomiting, sometimes coming on suddenly, and not always accompanied by nausea. As a rule, there is a moderate hypochlorhydria, with adequate response to histamine, which may account for the dyspepsia. The gastroscopic appearances have been described as being similar to those of pernicious anæmia, and as taking the form of atrophic gastritis, which improves on intensive liver therapy.

Anæmia may be pronounced even in the early stages, though more generally it develops when diarrhea has persisted for some time. It is a megalocytic, hyperchromic anæmia of the pernicious type, with alteration in the size and shape of the erythrocytes, very occasionally with normoblasts. Occasionally, severe anæmia, indistinguishable from that of Addisonian anæmia, with high Van den Bergh readings, supervenes even when active sprue symptoms have disappeared.

Tetany associated with dilatation of the stomach is quite common in longstanding cases, but is also found in the early stages where there has been dehydration of the tissues and hypocalcæmia. It can often be elicited

by compression of the upper arm (Trousseau's sign).

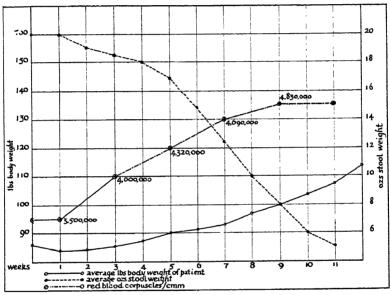


Chart 26.—Composite graph constructed from observations on ten cases, to show the relative increase in body-weight of patient and in red blood-corpuscles per cubic millimetre with coincident decrease in average weight of stool over the same period of treatment.

Cramps in hands and legs may be particularly distressing and are

the accompaniments of hypocalcæmia.

Diarrhæa.—Diarrhæa associated with sprue is of two kinds: one chronic and habitual, the other more acute and, in the early stages, evanescent. The former is characterized by one or more daily discharges of a copious, pale, greyish, pasty, fermenting, acid, mawkish, evil-smelling material: the latter is watery, also pale and fermenting, the dejecta containing undigested food and, as a rule, an abnormally large amount of fat and fatty acids. In these latter circumstances diarrhæa usually brings with it considerable relief to the dyspeptic distension—at all events for a time. When the mouth is inflamed, diarrhæa is usually more active,

but this is by no means invariable. The stools during periods of quiescence may be confined to one or two in the early morning or forenoon; during the later part of the day the patient is not disturbed. Even in this quiescent phase, however, they are always extraordinarily copious, the excessive bulk being attributable in great measure to fatty acids and to innumerable microscopic gas-bubbles. They are passed almost, or altogether, without pain. Not infrequently during exacerbations there may be a tender, exceriated condition of the anus; and sometimes, in women, a similar condition of the vagina, causing pruritus.

Types, history, course and termination. Primary or protopathic sprue.—There is a striking uniformity in the history of most cases of sprue. The patient has probably been suffering for months, or perhaps for years. from irregularity of the bowels. This, the physician may be told, began soon after arrival in the tropics, as a bilious morning diarrhea. For a long time this morning diarrhea went on, without interfering in any way with the general health. Later, the mouth now and again became tender, little blisters or excoriations appearing for a day or two at a time about the tip of the tongue or inside the lips. These sore spots would come and go. Perhaps, from time to time, exacerbations of the mouth symptoms would be associated with a little increase of diarrhea. Gradually, the stools lost their bilious character and became pale and frothy; dyspeptic symptoms. particularly distension after meals, now appeared. As time went on, these symptoms would recur more frequently, and in a more pronounced form. following, almost inevitably, any little imprudence in food or exposure. The general condition now began to deteriorate; emaciation, languor, lassitude, and inability to get through the day's work satisfactorily, becoming more pronounced each summer until, finally, a condition of permanent invalidism was established.

Should the disease continue to progress, the emaciation advances slowly but surely. Diarrhea may be almost constant, and now no longer confined to the morning hours; the complexion becomes dark, sometimes very much so; the appetite, at first in abeyance, may be ravenous, unusual indulgence in food being followed by increased discomfort, temporarily relieved by smart diarrhea. At length the patient is confined to the house, perhaps to bed. The feet become edematous, and the integuments hang like an ill-fitting garment, the details of the bony anatomy showing distinctly through the dry, scurfy, earthy skin. Finally, the patient dies in a semi-choleraic attack; or from inanition; or from some intercurrent disease. Such is the history of an ordinary, mismanaged case of sprue.

Another type of case commences as an acute entero-colitis or "hill diarrhæa," with sudden and profuse colicky diarrhæa, perhaps vomiting, and a certain amount of fever. The acute symptoms do not subside completely, but gradually acquire those of sprue grafted on to those of acute intestinal catarrh.

(a) Gastric cases.—Occasionally the morbid process is at first, judging from the existing clinical symptoms and subsequent history, confined to a limited part of the alimentary canal. Thus, there is sometimes sprue without diarrhea, the principal symptoms being sore mouth, dyspeptic distension, pale, copious but solid stools, and wasting.

- (b) Intestinal cases, incomplete sprue, para-sprue.—On the other hand, there are cases in which the mouth is not eroded, and there is little or no distension or dyspepsia, but in which the stools are liquid, copious, pale, and frothy. Sometimes a patient, who may have suffered at an earlier period or on a former occasion from the first type of the disease, later acquires the diarrheeic form; and vice versa.
- (c) Sprue without diarrhæa.—Sometimes under treatment the sore mouth, dyspepsia and diarrhæa completely subside; nevertheless, the wasting continues, the stools remaining phenomenally copious—so much so that the patient may declare that more is passed than has been eaten. In this case wasting is progressive, and the patient gradually dies of inanition.
- (d) Tongue or mouth sprue.—As a rule, the characteristic appearance of the tongue is associated with gastric and intestinal symptoms, but this is not invariable. The Editor has described some cases in Ceylon, and several others during the last twenty-five years, where the process remains confined to the mouth and gullet for a year or longer, before intestinal symptoms are noted. This stage may well be regarded as "larval sprue."

Intestinal atrophy consequent on sprue.—In certain instances, under treatment the symptoms proper to sprue subside, but the patient's digestive and assimilative faculties are permanently impaired. Slight irregularities, either in the quality or the amount of food, chill, fatigue, depressing emotions, and other trifling causes suffice to bring on dyspepsia accompanied by flatulence and diarrhœa. These cases may linger for years. Usually, they improve during the summer in England, getting worse during the winter and spring, or during cold damp weather. Ultimately, the patients die from general atrophy, diarrhœa, or some intercurrent disease.

Secondary sprue.—Sprue may follow closely on the heels of some other severe intestinal disease, such as amoebic or bacillary dysentery, or may be the direct sequel of hill diarrhoea. In bacillary dysentery, for instance, the sprue symptoms may be evanescent during convalescence, or, as sometimes happens, may become firmly established at some later period. Therefore, the recognition of a secondary form of sprue conforms with other nutritional diseases. The co-existence of intestinal amoebiasis with sprue has often been recorded.

Sequelæ. Ancemia and spinal symptoms.—Severe anæmia of the pernicious type is a frequent sequel (see p. 550). Until recently it had been generally considered that sclerosis of the spinal cord did not occur in sprue and that this distinguished it in some degree from subacute combined degeneration of the cord in pernicious anæmia. But this cannot always be substantiated, for in longstanding cases of sprue with severe anæmia, occasionally unmistakable signs of cord involvement—spastic paraplegia, ankle-clonus, positive Babinski sign, and, eventually, complete and fatal paralysis of the lower extremities—have been observed. Mild neuritic signs in the arms and legs (pins and needles) frequently supervene; sometimes also a generalized peripheral neuritis, with paræsthesia and loss of reflexes, resembling beriberi, which has been found to respond satisfactorily to vitamin B, therapy.

Œdema.—Generalized œdema, especially of the legs, is a frequent accompaniment of sprue, especially in those patients who are responding to treatment, and is probably connected with salt depletion.

Purpura.—Petechial hæmorrhagic rashes, noticeable on the thighs and legs (Fig. 62, p. 444) are a scorbutic phenomenon and formerly occurred in patients who had been fed on milk. This rash disappeared after the administration of adequate amounts of vitamin C. subcutaneous hæmorrhages on the hands are common in atrophic cases of

sprue and probably are scorbutic in nature.

Dermatitis.—A dermatitis is a frequent accompaniment of sprue. especially in elderly people with extreme anæmia. It generally breaks out during convalescence when the patient is responding to treatment. and is mostly seen on the arms and chest. Sometimes the rash is pellagrous. and the Editor has recorded cases of association of this disease with sprue. when improvement occurred on administration of nicotinic acid.

Special features of sprue in women.—Amenorrhœa and menstrual disturbances are extremely frequent in women with advanced sprue. Symptoms

of sprue usually become exacerbated during pregnancy.

Relapses of sprue are unfortunately frequent and form a characteristic feature of this mysterious disease. Often they come on suddenly, and quite unexpectedly, without any apparent exciting cause. Sometimes the typical relapses are observed after an interval of twenty to twenty-seven years of apparently normal health in England.

Latency.—One of the most remarkable features of sprue is latency. Thus, it may arise in England in persons who have at some time resided in an endemic area of the disease. Usually, this period is one or two years; sometimes it is longer—seven or eight years; exceptionally it may be as jong as twenty-five years.

Diagnosis.—The tongue, the stools, and the history seem sufficiently distinctive to render diagnosis easy. Cases do occur in which the disease has been diagnosed and treated as syphilis, the condition of the mouth being attributed to this disease, and the character of the stools and other symptoms ignored. Care must be taken in interpreting the significance of the smaller area of liver dullness usually found in well-marked cases of sprue. This is not due to cirrhosis of the liver, but to wasting, in common with other organs.

Differential diagnosis.—Cæliac disease (Gee's cæliac diarrhœa, or the Gee-Herter syndrome) occurs frequently in Europe in children under ten, and is also seen in those returning from the tropics. Cœliac disease is probably congenital and its ætiology is therefore different from that of sprue, but the stools are similar in appearance and in chemical composition. This disease is associated with diarrhea and meteorism, stunted growth, and incomplete sexual development. There is no involvement of the tongue and mouth, and the anæmia is not so severe as in tropical sprue. Symptoms usually disappear on a fat-free dietary. Idiopathic steatorrhea is probably the same process as coeliac disease persisting into adult life, and was described by Thaysen in Denmark and

Northern Europe as non-tropical sprue. This is a nutritional disturbance associated with tetany, osteomalacia, osteoporosis¹ and anæmia. It is therefore characterized by disturbances of the calcium metabolism and anæmia, which is usually hypochromic, but may sometimes be hyperchromic and megalocytic. According to Bennett, Hunter and Vaughan, in "non-tropical sprue" there are often cutaneous lesions, infantilism, megacolon, fine silky hair, brittleness and ridging of the nails, clubbed fingers, and a flattened type of blood-sugar curve after ingestion of glucose (which is also found in tropical sprue). Lens opacities, gross bony deformities, and tetany constitute the outward signs of defective calcium metabolism. The serum calcium is low and there is excessive excretion of fat. Both cæliac disease and idiopathic steatorrhæa may be complicated by secondary pellagra. An important, almost diagnostic, point of differentiation, is that these two forms of steatorrhæa do not respond to liver and folic acid therapy as does tropical sprue.

The absence of skin lesions and mental symptoms differentiates sprue from pellagra. The sprue tongue may be difficult to differentiate from that of pellagra; the latter is pointed, and when it is inflamed and painful the process is generalized, not confined to certain definite and circumscribed areas as in sprue. The "magenta tongue" of ariboflavinosis is distinctive. The tongue of early pellagra (Plate XVII) is invariably associated with angular stomatitis and an atrophic condition of the lips (cheilosis). Atrophy of the lingual papillæ also occurs in pernicious anæmia and so this may be confused with sprue. No difficulty should be experienced in differentiating Addison's disease from sprue. Gastrojejuno-colic fistula may give rise to symptoms simulating sprue, but these disappear when appropriate surgical measures have been undertaken.

The general picture may be mistaken for cholecystitis.

Giardiasis (see p. 539) may produce light-coloured fatty diarrhoea, and

may also be mistaken for sprue.

Differentiation of sprue from chronic pancreatitis may present difficulties. In the latter condition neutral fats predominate in the fæces, the tongue and mouth are not involved, and the diastatic reaction of the urine is high.

The low blood-sugar curve after the intake of 1 grm. of glucose per kilo. body weight serves to differentiate sprue from pernicious and allied anæmias, but a similar curve accompanies idiopathic steatorrhea and celiac disease. The anæmia of sprue greatly resembles that of pernicious anæmia, though normoblasts are rare and megaloblasts do not occur. High van den Bergh readings are the rule in true pernicious anæmia: exceptional in sprue. Differentiation from tropical macrocytic or nutritional anæmia cannot be made on blood examination alone, as the picture is very similar. This anæmia affects pregnant women in the tropics, and is not accompanied by diarrhea.

Certain cases of tabes mesenterica may, on clinical grounds, resemble sprue, and so may disease of the mesenteric glands, such as lymphosarcoma

or lymphadenoma.

The radiographic findings in sprue.—The radiographic features are those of a deficiency pattern. Films should be taken at half-hourly intervals

¹ Osteoporosis has never been recorded in tropical sprue.

after a barium meal. Fluorscopic examinations are made two or three times, usually with pressure films over the ileal region. Food is given five hours after the barium meal as soon as the barium has entered the cæcum. In early cases the mucosal folds of the small intestine may be reduced in number and appear more exaggerated, i.e., more irregular in width and spacing; but in advanced cases the mucosal folds may be entirely missing, giving rise to a smooth bag-like appearance or the "moulage sign." The mucosal changes are best seen in the jejunum.

Segmentation of the barium, the presence of discrete sausage-like masses, and irregular width of the lumen are seen as the barium passes through the small intestine. Small masses are left behind, giving rise to small clot-like shadows, more or less regular in shape and size which are most evident in the jejunum. The herring-bone pattern in this viscus described by American workers is not so common as it is in idiopathic steatorrhœa (Golden). These appearances, though characteristic, are not specific and have been attributed recently by Frazer and colleagues to over-secretion of mucus, which occurs in the small intestine. The results of a valuable investigation by Drew, Dixon and Samuel (1947), with a special barium mixture with fat, are in agreement with the above description, but the passage of a large fatty meal into the normal small bowel did not produce appearances similar to those of sprue, thus disproving the supposition that the changes are due to abnormal fatty contents. The radiological improvements always lag behind the clinical improvement after appropriate treatment.

Prognosis is good for recent cases, provided proper treatment is carried out. It is bad for patients over fifty, for longstanding cases, for careless and injudicious patients, and for those who cannot or will not take a special diet.

TREATMENT

General statement.—The treatment of sprue is mainly a matter of bodily rest and careful dieting in order to procure assimilation of the most easily absorbable foods. If treatment be undertaken sufficiently early, and be thoroughly and intelligently carried out, it is generally successful. Should, however, it be undertaken too late, when the glands and the absorbing surface of the alimentary canal have been destroyed, the case is almost sure to end fatally. In prescribing treatment, therefore, the first thing is to get the patient thoroughly convinced of the serious nature of his complaint; for without his hearty and complete co-operation a wellestablished case will not be cured. To be successful, treatment must be thorough, sustained and prolonged. All predisposing causes, such as uterine or other discharges, syphilis, and helminthic infections must, of course, be removed as far as possible. The size and weight of the fæces should be estimated daily by weighing the pan and subtracting from the total the known weight of the receptacle. The average daily weight of normal fæces is from six to eight ounces; in sprue it is commonly double or treble this amount. By keeping a chart of the average daily excretion, and by estimating the weight of the food ingested, an estimate may be formed of the daily intake and output.

Nursing of sprue cases is all-important. A great deal rests with the nurse; sprue patients are apt to be unreasonable and refractory, so she will need to be sympathetic and tactful, yet firm. A regular routine of feeding should be strictly adhered to, both in quantity and ingredients. The sheet anchor of treatment in sprue is diet, as all who have written on this disease agree. Fats and starches are not well assimilated.

Specific treatment.—The discovery of folic acid (folvite) and its instantaneous and beneficial effect on the outstanding clinical signs and symptoms of sprue has raised the hopes that in this substance we have at last obtained a specific remedy in such a dire and puzzling disease. The scientific grounds upon which this belief is founded have already been given (see pp. 545-548). Folic acid treatment should be commenced directly the diagnosis has been established. In tropical sprue its first effect is upon the glossitis and mouth symptoms which remit within a few days and give almost instantaneous relief. The appetite improves and, with the abatement of diarrhea and meteorism, there ensues a sense of well-being and a desire for food. In some patients this follows in a few days and they commence to regain the weight lost. Folic acid came into general use in 1946, and since then a large number of papers have appeared testifying to its efficacy. It is an expensive drug, hence the necessity of regulating a standard dose. It would appear that the larger doses which were first considered advisable are not necessarily essential. The curative dose ranges about 30 mgm. daily and the maintenance dose from 5-10 mgm. Folic acid treatment should be instituted directly the diagnosis has been arrived at, whether the patient is in the early or late stage of the disease.

When the patient is responding the imposition of a restricted diet does

not appear to be any longer necessary.

The following doses of folic acid are provisionally suggested:—30 mgm. daily for 10 days; 20 mgm. for a further 10 days—thereafter 5 mgm. daily as maintenance dose.

In order to obtain the maximum hæmatological response folic acid must be combined with intensive intramuscular liver therapy. Spies and colleagues have found that a compound—5 methyl uracil, or thymine—can be substituted for folic acid, but large doses are necessary, i.e., about 6 grm. daily for 14 days as compared with 20 mgm. of folic acid.

Teropterin (Pteroyltriglutamic acid) has been tried out by Suarez and colleagues in a series of five patients. Four received 10 mgm. intramuscularly and one 20 mgm. The reticulocyte response was maximal. A daily dose of 10 mgm. is equivalent to 6.3 mgm. folic acid and is probably adequate.

Vitamin B_{12} , a red crystalline substance obtained from the liver, is considered by some to represent the intrinsic factor. A similar substance has been obtained from cultures of *Streptomyces griseus*. The activity has been estimated on cultures of *Lactobacillus lactis*. Totter suggests a dose of 3 μ grm. daily for six weeks.

Treatment of anæmia.—In extreme cases with blood destruction in which the blood picture resembles that of advanced pernicious anæmia,

blood-transfusion is essential and some with a red cell count of half a million r.b.c. per c.mm. have recovered. Sometimes two or three trans-

fusions at weekly intervals are advisable.

The beneficial effects of liver soup in sprue have been noted since the early days of Manson and van der Burg. The best preparations of liver suitable for oral administration are those of Eli Lilly, Parke Davis, and Oxo (Liveroid), but large quantities are required, and they are expensive. An important advance is intramuscular injection. Campolon (Bayer), Hepatex, Plexan and Examen are most efficient. In grave cases 4 ml. is injected daily for six injections, but usually a series of 12 injections of 2 ml. suffices. They should be made deep subcutaneously into the buttock, and are usually followed on the ninth or tenth day by a rise in the reticulocyte count. The first injections may be rather painful, but this gradually works off as more are given. Sometimes the addition of iron is of advantage, especially in cases without megalocytic blood changes. It may be given in the form of ferrous sulphate tablets (Glaxo) three times daily, or of hæmatinic plastules (Wyeth).

Other vitamins.—Some cases of sprue improve on liberal administration of vitamins, such as nicotinic acid and riboflavin, but a combination of vitamins is indicated such as *Beplex* (Wyeth) which contains aneurin, riboflavin, nicotinic acid, pyridoxin, and pantothenic acid.

Diet.—Much has been written about the details of a sprue dietary and most varied opinions have been expressed. When the tongue and mouth are very sore the patient is fed on milk, and should this not be well tolerated on Sprulac (p. 561). Horlick's and Benger's preparations are also suitable. A high protein dietary, as advocated for pernicious anæmia, is preferred by some authorities. In the second week the patient may be allowed three pints of milk daily, with rusks or toast, a lightly boiled egg, minced chicken, sweetbreads, minced liver, semolina, ground rice and tapioca puddings. Junket is also suitable. Amongst fruits, bananas and baked apples are well tolerated. Formerly mystical properties were attributed to strawberries and bael fruit (Aegle marmelos) in the treatment of sprue. Both are suitable when they can be procured. Raspberries and blackberries are also relished by the patient.

The principle of sprue dietary is avoidance of fatty or greasy foods

and the ingestion of too much carbohydrate.

In elderly patients (i.e., those over 45) and where there is a high degree of anæmia, the addition of raw or underdone, finely shredded beef is of advantage.

Minced beef for Sprue Patients 8 oz. best beef; 1 good teaspoonful of marmite; Pepper and salt; 2–3 tablespoonfuls of water.

Trim off all fat from the beef. Mince the raw beef finely, putting it twice through the mincing machine if necessary.

Place in double saucepan with marmite, seasoning, and water. Cook over

boiling water, stirring the ingredients with a fork all the time until the meat has turned brown and crumbly—roughly 3 minutes.

Serve on a hot-water plate. Treated in this manner minced beef is a palatable dish.

In patients with flatulence and meteorism which are increased by milk, this beef diet may be substituted for one pint of milk.

Lightly-steamed meat with gravy is advantageous, and should be steamed in the following manner:

Take undercut of beef, 4 oz. Steam with 6 oz. of water for 5 to 7 minutes. Add a pinch of salt and serve as thick soup with lemon juice or slice of tomato.

The recipe for liver soup is as follows:

Take half a pound of calves' liver and cut it into small pieces. Place in a double saucepan, add $\frac{1}{2}$ pint of cold water and simmer for $1\frac{1}{2}$ hours. Strain through a sieve and add 1 pint of bone stock or chicken jelly, and, if necessary, flavour with marmite. Add a small quantity of pepper and salt.

Liver soup can be given in soup-platefuls of 8 oz. each, and may be taken together with underdone meat.

Food should never be given unless the patient is hungry. It is a great mistake to try to let these patients eat quickly, or to stimulate the desire for food by encouraging active exercise. The bowel is not in a condition to deal with large meals.

A high-protein milk powder, or Sprulac (Cow & Gate, Ltd.) is prepared from fresh milk which has been treated by passage through a gauze and wire filter, subsequently chilled, centrifuged to get rid of organic and inorganic débris, passed through a mechanical mixing apparatus and eventually desiccated at 120° C. The powder contains 10.6 per cent. fat; 34.0 per cent. protein and 45.0 per cent. lactose. The calorie value per ounce is 125 and the ratio of protein, fat and carbohydrate is 1.0: 0.3: 1.3. Sprulac can be given in the same manner as milk. One ounce of Sprulac is made up to 8 oz. with water and given every 2½ hours for six feeds. Subsequently the amount may be increased and calves'-foot jelly and the juice of two oranges added. Sprulac forms an excellent addition to the diet in all stages of sprue.

Dehydration.—Dehydrated cases must be treated on modern lines with fluid replacement therapy by intravenous drip saline. Treatment by increasing the salt intake to 15 grm. daily combats the dehydration, usually in a few days. Checking the diarrhea by the use of sulphaguanidine or sulphaguacidine is most important.

Return to Europe.—When sprue develops in the tropics, if feasible, the patient should be sent to Europe as soon as possible. It is a mistake, however, to ship an invalid if the disease is active, or the end manifestly not far off. Diarrhea should not be present when the patient is put on board ship. The effect of folic acid in a hot climate appears to be equal to that observed in Europe, and this necessarily has exerted a considerable influence on the management of this disease in the tropics.

Clothing and general management.—Sprue patients returning to Europe ought to be especially careful in their clothing, and they ought to get out their warm clothes before the ship leaves the tropics. If they return during the winter, they should arrange to remain in the south of Europe until late spring. Next to an unsuitable dietary, perhaps cold is the most prejudicial influence to which a sprue case can be exposed. A sprue patient

ought never to feel cold; he ought always to wear thick flannels, thick stockings, and, when up and about, thick boots. In winter a chamois-leather sleeved waistcoat is of great service. His rooms ought to be warm. He ought to eat very sparingly. He ought never to be fatigued; he ought to go to bed early and rise late; in fact, he ought to do everything in his power to avoid irritating the bowel, to guard against chill, physiological depression, and copious eating.

During the summer England is suitable enough as a residence; but during the cold winter and spring months some milder, drier and more

sunny climate must be sought.

Sore tongue and mouth.—This responds readily to folic acid treatment, but a great deal can be done to ameliorate the soreness and the dysphagia caused by ulceration of the tongue and mouth. The mouth should be kept very clean and washed out after each feed with a bland mouth-wash such as potassium chlorate, 1 drachm to the pint of hot water, but if the mouth is very painful, cocaine, 2 gr. to the ounce of glycerin and borax, brushed on to the tongue lightly before eating, will deaden sensibility. In certain cases where the saliva is very acid, as it generally is when the tongue is very raw, an alkaline mouth-wash should be used as follows:

Sod. bicarb. gr.x (0.648 grm.) Sod. biborate gr.x (0.648 grm.) Rose-water 3iv (113.6 c.c.) Diluted with water according to taste.

In cases with marked hypochlorhydria the administration of hydrochloric acid is advisable. A mixture containing 20 min. of the dilute acid should

be given before each main meal.

Diarrhea.—The diarrhea of sprue yields to dietetic treatment but, if excessive, the best method is to administer a small quantity of castor oil in teaspoonful doses, after which kaolin powder in the same quantity should be given, suspended in milk or water. If nocturnal diarrhea is very severe, chlorodyne (10–15 min.) is often successful. Sulphonamides, especially sulphaguanidine and sulphasuccidine, in full doses of 5–10 grm. daily, according to the patient's weight and tolerance have proved very successful in checking sprue diarrhea.

Flatulence and meteorism.—In cases with extreme distension injection of pituitary extract, especially pitressin ($\frac{1}{8}$ -1 ml.), is followed by passage

of flatus and instant relief.

Constipation.—The constipation following the acute phase of sprue may be difficult to overcome. Often hard scybala form in the sigmoid colon and become impacted. The best aperient is castor oil. In extreme cases it may be necessary to give an enema of warm olive oil (10 oz.) and subsequently to remove the scybala from the rectum by the finger. As a general aperient, petrolagar (red label), or agarol, are preferable to liquid paraffin.

Anal excoriation and irritation is sometimes a distressing feature, and

may be relieved by the following ointment:

Orthoform			•		40 gr.
Zinc oxide					120 gr.
Starch .					120 gr.
Paraffin .			 	ad	l oz.

Tetany and cramps.—The treatment of these symptoms, which are due to calcium deficiency, is by administration of calcium by the mouth in doses of 10 gr. three times daily, and in extreme cases by intravenous injection of salts, such as calcium gluconate (Sandoz) 10 ml. or over.

To increase assimilation in atrophic cases.—Glucose, 2 oz. daily, should be added to the dietary throughout; and to increase assimilation when intestinal atrophy is a feature, insulin, 2-6 units, injected twice daily, may often be followed by an increase of the appetite and a corresponding aptitude for absorption.

Anorexia and vitamin B_1 deficiency.—The loss of appetite and taste in severe cases of sprue is a difficulty, but usually improves gradually when the patient is put to bed. It has been found that vitamin B_1 (aneurin) increases the desire for food; it may be injected, in doses of 25 mgm. daily, with advantage. It is curative also in cases presenting neuritic symptoms with loss of deep reflexes.

Convalescence.—Sprue patients, if possible, ought not to return to the tropics. Young adults often recover completely, but the danger of relapse is greatly enhanced in those over 50 if they return to a hot country, especially India. If compelled by circumstances to do so, they must exercise the utmost care for their health, and avoid exposure, cold baths, and all excesses; purge gently, and go on simple diet on the slightest sign of relapse. Alcohol, especially strong spirits, is strictly contra-indicated for at least three months from the time of apparent recovery. A maintenance dose of 5 mgm. folic acid is recommended.

Treatment of complications.—Careful search should be made for any co-existing infection from which the patient may be suffering. Malaria, especially benign tertian, and, more important still, syphilis, may prejudice recovery. Sprue patients with syphilis tolerate antisyphilitic treatment well and their general condition is benefited. Sprue may be complicated by amæbic dysentery, and in such cases vigorous treatment with emetine and emetine-bismuth-iodine may be necessary before any improvement in the general condition is noted. Acute appendicitis quite commonly complicates sprue and may necessitate operation, with the result that the underlying sprue is improved. Sometimes acute lobar pneumonia may supervene, and it has been noted that the sprue symptoms have been much improved after recovery.

HILL DIARRHEA

Little has been heard in recent years about hill diarrhea. It is a form of morning diarrhea accompanied by flatulent dyspepsia and the passage of copious liquid, pale, frothy stools. It occurs principally in Europeans on visiting the hills after residing for some time in the hot lowlands of tropical countries. Hill diarrhea is a frequent precursor of the fully developed disease—tropical sprue—and probably is of similar ætiology.

Crombie, who gave an excellent account of this disease in India, pointed out that a similar affection may show itself in the highlands of Europe, Africa, and possibly South America, and Steen described a similar diarrhœa in Java, where it is known as "Bandoeng sprue." There is no reason, therefore, to suppose that hill diarrhœa is peculiar to India, although, owing to the large European

population frequenting the hill sanatoria in that country, it has been particularly noticed there. An elevation of 6,000 feet or over, when combined with an atmosphere saturated with water vapour, is particularly favourable to its development. In India it is found to begin and end with the rains, during which, in certain years and places, it is apt to assume almost epidemic characters. In some years hill diarrhea is less prevalent than in others; but at the proper season few of the various hill sanatoria of India are without cases.

Without very obvious cause, the patient, who in other respects may be in good health, soon after arrival at a hill sanatorium becomes subject to a daily recurring diarrhæa, the looseness coming on regularly every morning some time between 3 and 5 o'clock. The calls to stool are apt to be sudden and imperative. The motions passed are remarkably copious; very watery in some instances, pasty in others. They are pale, frothy, and like recently stirred whitewash, so devoid are they of biliary colouring matter. Their passage is attended with little or no pain, often with a sense of relief. From one to half a dozen, or more, such stools may be voided before 11 a.m. After that hour—at all events, in ordinary cases—the diarrhæa is in abeyance for the rest of the day, and the patient may go about his duties or pleasures without fear of inconvenience.

Treatment.—In view of the discovery of folic acid the older ideas of treatment will have to be revised. The diarrhœa generally yields to strict diet—milk and junket, warm clothing and removal to a lower altitude. The diarrhœa is checked with sulphaguanidine or sulphasuccidine in full doses as well as the administration of folic acid.

Section IV.—INFECTIVE GRANULOMATOUS DISEASES

CHAPTER XXXIV

LEPROSV

Definition.—A chronic infective granulomatous disease produced by the leprosy bacillus, characterized by lesions of skin, nerves and viscera, ending in local anæsthesia, ulceration and trophic lesions. After a prolonged course it is usually fatal.

Epidemiology.—Various estimates have been made of the total number of lepers in the world. From official figures, admittedly incomplete, they number about 3,500,000, but this is undoubtedly an underestimate, and the true figure is probably about four to five millions. The most striking fact brought out by Rogers and Muir, in their study of climatic factors, is that every country with a high rate of incidence (5 per mille and over) is in the tropics and possesses high annual rainfall and a considerable degree of humidity. The state of civilization and culture amongst these coloured peoples is low, and they live in small overcrowded houses under conditions of semi-civilization favourable to the spread of this disease.

The highest incidence is found in tropical Africa. The estimated rates per mille of population are 20 in Belgian Congo; 16 in French Equatorial Africa, and 5–10 in the British West and Central African colonies. In tropical Asia and Oceania a high rate of prevalence occurs, with rates varying from 2–22 per mille (New Caledonia and the Marquesas). In the Western Hemisphere the incidence varies from 1 in the West Indies to 3.75 in Colombia, Venezuela and Brazil. The world-wide relation between rainfall and leprosy incidence is seen in the noteworthy fact that leprosy is almost completely absent from those parts of the tropics with a rainfall of less than 10 inches per annum.

In temperate climates and in North Europe the rate appears to be nowhere over 1 per mille with the exception of parts of India, China and the Southern portion of Japan, in areas with a comparatively high rainfall. The explanation of these basic facts appears to be that dry heat is inimical to the survival of the lepra bacillus outside the human body. According to Rogers and Muir, the evidence of accumulated data favours the view that the organism generally invades the body through the skin.

Rogers has furthermore suggested that mild tuberculization of a community producing an exalted immunity to the tubercle bacillus also affords some protection to leprotic invasion, although the reverse is certainly not the case, as it is common knowledge that lepers often succumb to pulmonary tuberculosis.

Predisposing factors.—The most important factors influencing the prevalence of leprosy are a low stage of civilization and accompanying grave hygienic defects. This was shown by the disappearance of leprosy from amongst a number of infected Norwegian immigrants into the United States when leprosy died out as a result of the greatly improved hygienic

conditions under which they lived. It has become clear, moreover, that there is little or no tendency in leprosy to spread at the present day under favourable hygienic conditions in temperate climates. Defective housing and overcrowding furnish favourable conditions for its spread, and in the main endemic areas the poorer inhabitants live in close proximity to one another. One fact that has been brought out strongly in the Hawaii reports is the effect of irregular sexual relationship with native women, and in the Marquesas Islands epidemic leprosy was spread by the prevailing promiscuity. Sociability, too, has been found to favour its spread; thus, in Norway Hansen recorded that formerly it was considered impolite to refuse to sleep in the same bed as a leper, if he was not in an advanced and noticeable stage of the disease. The habit so prevalent in the Pacific Islands of smoking communal pipes and of eating out of the same dish naturally also favours infection. Absence of fear of the disease. as in native tribes of Central Africa and in the Pacific, and their objection to isolation of lepers naturally encourage direct contagion.

Diet is said to predispose to leprotic infection, especially the edible

vam root—colocasia—in the Pacific Islands.

Epidemic diseases, such as typhus or plague, attended by a high general mortality, have in the past resulted in great, though temporary, decrease

in prevalence of leprosy.

Ætiology.—The universal and ancient conviction of the infectious nature of leprosy is accepted everywhere, but during the nineteenth century there existed a deep-rooted belief in the almost exclusive origin of leprosy through heredity. Native belief for centuries in China, Japan and Central Africa has been moulded on the heredity theory, but it was held that this

taint does not make its appearance until puberty.

In St. Kitts Munro found, in 64 cases with reliable family records, that there was no family history in 34, whilst of the remainder there existed a direct history in 9 only. During the past decades much positive evidence has been obtained against the heredity theory. First, there is the diminished fecundity of lepers, which is well known. The rapid increase of leprosy in Hawaii could by no means be explained on any hereditary basis. The most striking example, however, in history is the observations of Hansen on 170 Norwegians who migrated to Minnesota, U.S.A. when suffering from the disease; not one of their descendants, up to the third generation, had contracted leprosy in America.

Contagion.—It is generally accepted that leprosy is conveyed from the sick to the healthy by contagion, and this is emphasized by all who have written on this subject, such as Brousse in Trinidad (1879), Hills in British Guiana (1881), and Leloir in the Hawaii reports of 1886. A native of a non-leper colony may acquire the disease on visiting a leper country and, moreover, may communicate it to his fellow countrymen on his return. One well-authenticated instance occurred in 1872 when an Irishman, who became a leper in the West Indies, returned and conveyed it to his brother in Dublin. The Editor studied a somewhat similar case in a woman whose husband—a Mauritian—had died of leprosy, and who developed the disease in London, where she had lived all her life, after an incubation period of seven years.

Intimate contact appears to be necessary, combined with lowered resistance and susceptibility to infection, because implantation of the bacillus does not alone suffice. Many attempts have been made in the past to communicate leprosy to man by inoculation; all, with two questionable exceptions, have failed. De Langen (1936), however, reported the case of a European in Java who was injected with morphia from a syringe previously used on a leper; six months later a leprous nodule appeared on the forearm at the exact site of the morphia injection; subsequently, other lepromatous manifestations were noted. In June, 1936, Lagoudaky was twice inoculated intramuscularly with leper blood. Some forty-four days later two small subcutaneous leprous lesions appeared and he was demonstrated in 1938 at the International Leprosy Congress.

The rapid spread of leprosy in a susceptible community is difficult to reconcile with the statement that in many instances contact under favourable circumstances has failed to convey the disease. Thus, in those who have lived for a long time in attendance on lepers there have been only a very few instances of infection, e.g. the historic cases of Father Damien at Molokai, two Sisters of Mercy and the Medical Superintendent at Robben Island in South Africa. But hundreds of attendants on lepers pursue their work for years unscathed. In Louisiana 19 Sisters of Charity have been in attendance on lepers for 41 years without one single instance of infection.

As with tuberculosis, evidence points to the susceptibility in early life. The relationships involving intimate contact in childhood are most important. This has been realized in the Culion Island leper colony (Philippines) where children of lepers removed from their leprous surroundings do not contract leprosy. Amongst 10,000 lepers there Denny noted that 35 per cent, were brothers and sisters, 27 per cent, cousins, 11 per cent, children of lepers, 7 per cent, parents of lepers but only 1 per cent, husband and wife. In Japan it is recorded that 7 per cent, of children of lepers contract the disease. The childhood rate is the number of child lepers per 100 cases of leprosy.

It is held that the two main signs that leprosy is diminishing in any area are a high lepromatous type rate and a low child rate. Most statistics show that leprosy is more common in men than in women at about 2:1. Usually leprosy is much more common in the poorer and less hygienic classes.

Bacillus lepræ (Mycobacterium lepræ).—This organism is the accepted cause of leprosy and is present usually in great profusion in the tissues. In size, shape and staining reactions it closely resembles the tubercle bacillus. It exhibits marked pleomorphism; the ends are somewhat attenuated and by some it is said to possess a gelatinous capsule. Individual bacilli vary in size, from 1.5 to $5~\mu$ in length and from 0.2 to $0.5~\mu$ in breadth. Curved forms with pointed ends are not uncommon. In the reactionary stages of the disease the organisms may be granular, coccoid, mono- or bipolar. Round, spore-like bodies often impart a granular appearance to a clump of bacilli. In common with the tubercle and smegma bacilli Myco. lepræ is acid-fast, retaining carbol fuchsin stain after being treated with mineral acids, though it may be distinguished from

Myco. tuberculosis by being more easily decolourized by alcohol than by weak acids. Moreover, it occurs in large numbers in the lesions, chiefly in zooglea masses within the lepra cells, often grouped together like bundles of cigars or arranged in a palisade. Chains are never seen. Most striking are the intracellular and extracellular masses, known as globi, which consist of clumps of bacilli in capsular material. (Fig. 82.)

The bacilli can be readily demonstrated by excision of a leproma, or they can be obtained by clamping a nodule, pricking the solid tumour, collecting a droplet of expressed "leper juice" on a coverslip and staining by the Ziehl-Neelsen method. They are Gram-positive. They are found

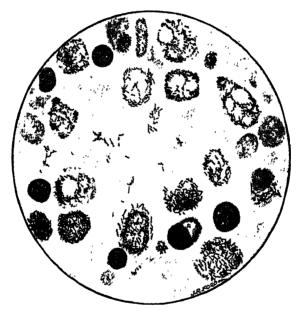


Fig. 82.—Section of spleen showing lepra cells and lepra bacilli. × 800.

in all primary deposits, in the skin lepromata, in marginal infiltration of the macular eruptions (where they may be very sparse), in apparently normal skin in the vicinity of leprous lesions, in the early stages of leprous neuritis (where also they may be present in small numbers) and in the specific lesions in the liver, spleen, testes and lymphatic glands. In the blood vessels they have been found in the endothelium and occasionally free in the blood, or engulfed by leucocytes. This fact is specially useful in diagnosis when thick dehæmoglobinized blood-films are stained by Ziehl-Neelsen stain. Bacilli are also abundant in the purulent and mucoid discharges from the nose, as well as from ulcerating lepromata. Very rarely have they been found in the spinal cord or lungs.

Cultivation of Myco. lepræ, though repeatedly attempted, has never been really successful. Some investigators, it is true, have obtained growths of

acid-fast bacilli (chromogenic and non-chromogenic), or diphtheroids, which in some instances have developed acid-fast forms on subculture. Others have described branching bacilli, granular and coccoid forms.

It is probable that all four varieties (diphtheroid, pigmented acid-fast, apigmented acid-fast and acid-fast streptothrices) have been more or less commonly encountered in leprous tissue in various parts of the world. When some of these cultures are injected, transient granulomatous lesions have been obtained, but there is general agreement that they do not constitute true leprotic lesions.

Inoculation of animals with human leprous material containing prodigious numbers of organisms does not give rise to typical progressive leprous lesions. Adler (1937) succeeded, to a limited extent, in communicating leprosy to young splenectomized Syrian hamsters (Cricetus auratus). A fragment of lepra nodule was inserted under the skin and, when the animal was later killed, leprosy bacilli were demonstrated in the liver, and (in other animals) in neighbouring enlarged and caseating glands, but he failed entirely to carry on the disease by subinoculation in a continuous series of hamsters. Similar results have been obtained by Burnet. Subsequently Dharmendra and Lowe in India, in a series of carefully planned experiments on the same animals, by implantation into the abdominal wall and intraperitoneal inoculation, failed to produce generalized or progressive infection. When the nodule was implanted into the abdominal wall, masses of bacilli were found at the site of the implant, but not beyond, and bacilli were found elsewhere in two animals only. The fact seems to be that lepra bacilli can survive for long periods in inoculated animals, even dead bacilli may evoke local reactions and produce pathological appearances similar to those produced by living organisms. Araujo in Brazil appears to have had experiences similar to those of Adler and to have found the organisms in the European hamster (Cricetus cricetus) in great profusion. Collier (1940) implanted lepromatous material beneath the skin of monkeys fed on a diet of Colocasia (Yam) over a long period. is claimed that some developed symptoms reminiscent of leprosy in man and that acid-fast bacilli were obtained from material procured from the ears of these animals. Cochrane, Menon and Pandit, on repeated injections of splenectomized monkeys with human leprosy material, found that they developed strongly positive lepromin reactions. Cochrane considers that M. lepræ cannot parasitize the reticulo-endothelial system, unless it multiplies in the corium of the skin. Hanks attempted to cultivate leprosy bacilli in small cubes of leprous tissue placed in various fluid and solid culture media, as well as by injection of leprosy material into chick embryos and chick tissue cultures. No evidence of proliferation of the bacilli was obtained.

Rat leprosy.—A leprotic disease of the rat, which occurs naturally throughout the world, was first observed by Stéfansky in Odessa in 1903. Two types are recognized: disease of skin and muscle and disease of lymphatic glands. In tropical rats it occurs commonly and has been specially studied by Lampe and de Moor in Java. House rats are usually affected, especially R. rattus concolor and R. decumanus. Infection in these animals is conveyed by injury and by cannibalism. Laidlaw

succeeded in transmitting this disease to the Syrian hamster, and it can also be conveyed to rats of the same species, infection taking place readily through skin abrasions and subcutaneous inoculation. The bacillus is Mycobacterium lepræ murium, morphologically indistinguishable from Myco. lepræ, whilst the lesions resemble those of human leprosy, macroscopically as well as histologically. Attempts at cultivation have shown much the same negative results as in human Myco. lepræ.

Fielding has demonstrated numbers of bacilli in the urine and fæces of rats, and has proved that ancylostome larvæ can take up these organisms from the fæces and introduce them into the skin. Repeated inunction of

the healthy skin will, moreover, produce infection.

In spite of the general similarity of human and rat leprosy, it is generally agreed that the organisms represent two separate and distinct species and there does not seem to be any connection between this disease of the rat and human leprosy.

Pathology.—Spread of leprosy through the body.—Myco. lepræ enters the skin, either by direct inoculation, or by spread from another focus, possibly carried by wandering cells. Passing through the capillary walls, the bacilli lie in the perivascular lymphatics or are ingested by endothelial cells and histiocytes. The process is difficult to follow in the case of macules with scanty bacilli, which spread centrifugally. The bacilli pass from the cutis to the main nerve trunks by the lymphatic channels and are found lying singly or in groups between the nerve fibres. Metastatic spread through the bloodstream and auto-inoculation through abrasions also occur. Bacilli have been found in the corium of the skin over almost the whole body. It was formerly supposed that they were absent from the soles of the feet and palms of the hands, but this is incorrect; macroscopically, the lesions are inconspicuous in these situations owing to cornification of the skin.

In advanced lepers the mucous membrane of the nose, mouth and pharynx are affected, and the eye frequently, both superficially and deep. The lungs, even in the most advanced stages, escape to a great extent. The liver is usually invaded, and bacilli are found in the interlobular connective tissue and around the central veins. The interstitial Kupffer cells are swollen with bacilli, which, however, do not penetrate the parenchyma cells.

In acute advanced cases the spleen is often involved, especially in the arterial sheaths and the Malpignian bodies. The glands at the hilum are frequently infiltrated. Small numbers of bacilli have been demonstrated in the esophagus, stomach and intestine, with involvement of corresponding lymph glands. Absence of intestinal ulceration, as a rule, characterizes leprosy. In nodular leprosy the bacilli may be present in the glomerulus of the kidney, when they may cause hyaline degeneration and interstitial nephritis, which is quite common in leprosy.

In a large proportion of cases of nodular leprosy of prolonged duration amyloid or lardaceous disease of the alimentary canal, liver, spleen and kidneys ensues. Taylor (1945) has shown that relatively benign leprous infiltration of the submucosa of the gastro-intestinal tract may take place.

In lepra reactions this infiltration may undergo necrosis producing ulceration, as in Reisner's case (1896).

The suprarenals are attacked in all cases in which the liver and spleen are affected. The testicles are to a great extent destroyed in all nodular cases by inter- and intra-tubular invasion.

Leprous affection of lymphatic glands is histologically obvious. The glands are swollen, but without alteration of form. On section, the ampulæ and medullary cords are yellow, or yellowish-brown, which renders them unmistakable. The inguinal glands are especially affected and the



Fig. 83.—Egyptian child, aged 11, showing acute early nodular leprosy. (Dr. H. K. Giffen.)

lower members of the group may be as large as pigeon's eggs. Microscopically, the ampulæ and trabeculæ are filled with globi: evidently lymph cells which have become filled with bacilli. The circulation through the glands is not arrested; nevertheless, they retain their infectious products. Suppurating lymph glands are not infrequently found in skin leprosy, especially in the groin and neck. On the other hand, especially in the Pacific Islands, these glands may be tuberculous, or may even contain both leprosy and tubercle bacilli.

Distribution of bacilli in skin and nerves.—In the skin the leprosy bacilli may be destroyed by the tissues of the body; they may be latent, or they may multiply and spread. The vessels of the corium are arranged in two plexuses: the superficial, or subpapillary, and the deep or subcutaneous. These communicate through vessels adjacent to the hair-follicles and

sweat glands. The subpapillary plexus supplies branches to the papillæ; the deep communicates with arterial and venous vessels lying in the subcutaneous tissues. Nerve-plexuses correspond to those of the vascular

system.

The spread of leprous infection in the corium takes place in the lymphatic channels. In some lesions the superficial plexus and its papillary branches are involved: in others the whole thickness of the corium. In others again, spread is primarily along the deep plexus, invasion of the superficial layers taking place along the hair follicles, resulting in the pebbly appearance of some tuberculoid leprosies.



Fig. 84.—Nodular leprosy in an Egyptian. (Photo, Dr. H. K. Giffen.)

The central nervous system is seldom the site of leprous lesions. When secondary degeneration of the spinal tracts takes place it is due to extreme destruction of peripheral nerves, but the spinal and Gasserian ganglia have been found to contain bacilli. Septic abscesses of the larger nerve trunks, especially the ulnar, are sometimes found.

Wherever leprotic infection advances there is a general or local reaction on the part of the tissues to arrest the invasion. In the lepromatous type this reaction is generally limited, but in the neural it may be pronounced, and the leprotic process may remain for years confined to a

single lesion.

Pathology of lepromatous (nodular) lesions.—Young lepromata present a smooth, white, glistening appearance on section, but the older appear browner. The specific lesions of leprosy differ from those of tuberculosis, inasmuch as they are well supplied with blood vessels, and never undergo caseation. The earliest recognizable lesions are generally multiple, the

result of bacillary metastasis from some unknown reservoir. The more acute the process, the more numerous the foci. Lesions are classifiable as nodules, papules, macules and diffuse infiltration.

Nodules, round elevations of skin of limited size, may be temporary or permanent, soft vascular or fibrous. The nodule is probably formed at the site of a bacillary embolus, either in normal skin or in a portion already infiltrated with leproma. (Figs. 83, 84.)

Papules are smaller than nodules, not larger than a split pea.

Macules are roughly circular or elliptical patches of discoloured skin, and are found in both the main types of the disease.

Diffuse infiltration of the skin is often noted without the appearance of nodules or macules. It is due to infection of the skin at numerous points accompanied by cellular infiltration, but response to the invading bacilli is insufficient to produce clinically noticeable signs. In resolving lesions the skin may assume a thin atrophic appearance resembling crushed parchment.

The essential cell in defence against leprosy is the macrophage

(histiocyte).

There seems to be an allergic element in tissue response in leprosy. The early reaction to *lepromin* is probably allergic, but it is not clear that the late, true reaction is the same. The lepromin test is usually negative in lepromatous cases, positive in tuberculoid and nervous cases, and usually positive in child contacts, especially in the later years of childhood.

When the resistance of the individual is high, characteristic histological changes are: concentration of round cells, especially round hair follicles and vessels and development of the "tuberculoid focus," similar to tuberculosis. The essentials in the histology of the skin in resistant or neural leprosy are: localization of the process in the skin, the foci being chiefly perifollicular and perivascular; formation of epithelioid and giant cells; invasion of the subcutaneous nerves.

The histopathology of the nerve lesion corresponds to that of the skin. In advanced lepromata bacilli and lepra cells are more abundant and there is formation of fine fibrous tissue in the endoneurium which may later contract and block the nerve-fibres. In the neural type bacilli are few, though it is easier to find them in nerves than in the skin. The cellular reaction also tends to be more intense, so that epithelioid and giant cells are present in greater or lesser numbers surrounded by small round cells. Thickened nerve trunks may become enclosed in a dense fibrous sheath which may later cause constriction.

In the non-resistant case the essential cell is the macrophage but, as the bacilli multiply, so no attempt is made to localize infection, owing to the relatively lowered resistance of the tissues. The bacilli multiply rapidly, the macrophages become active and phagocytose the bacilli. These are the "lepra cells" which are uniformly distributed beneath the epidermis (see Fig. 82, p. 568).

In lepromatous leprosy there is no centralization of "lepra cells" in the granuloma; nerves in the cutis stand out and do not appear to be invaded.

As this process continues, the invasion of the cutis becomes more intense, and all the skin elements become involved and eventually unrecognizable, so that the epidermis becomes flattened, and the whole subcutaneous tissue, including the subcutaneous fat, is invaded by the granuloma. The lepra cells now appear to give up the attempt at phagocytosing the bacilli and undergo a curious foamy degeneration (foamy cell of Virchow). There is marked absence of gross invasion by lymphocytes. Owing to the ease with which the bacilli multiply they are carried by the lymphatics throughout the body and there is general dissemination and multiplication, especially in the reticulo-endothelial system (Fig. 85).

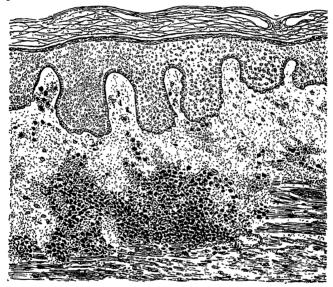


Fig. 85.—Early lepromatous lesion, showing diffuse infiltration of subpapillary, and dense infiltration of sub-epidermal layers.

Pathology of tuberculoid lesions.—The epithelioid cell is distinctive of the tuberculoid lesion, not only in the skin, but also in the nerves; it seldom, if ever, contains lepra bacilli. Indeed, it is usually difficult, or quite impossible, to find bacilli in this type of lesion. The so-called "giant cell of Langhans" is another characteristic, and occasionally a few bacilli are found in connection with it. This cell may be of considerable size and is found in skin and nerve tissue surrounded by numbers of small lymphocytes. In typical tuberculoids the cellular elements are arranged in dense cords, which in section resemble tubercles (Fig. 86).

The activity of lesions is indicated by abundance of typical epithelioid cells, and in major tuberculoid the inflammatory process may be so acute that necrosis and ulceration of the skin take place.

Immunity.—Contrary to the popular belief, there seems little doubt that there is a natural immunity to infection which varies in degree in different

individuals. Susceptibility to infection may depend upon general health, because it is certain that debility from any cause lowers resistance to leprosy. Varying individual resistance is also exemplified by the type of the disease. The nerve type, with tuberculoid lesions and few bacilli, indicates a comparatively high resistance, and the multibacillary lepromatous form a comparatively low resistance. In the former, Mitsuda's skin (lepromin) test is usually strongly positive; in the latter negative.

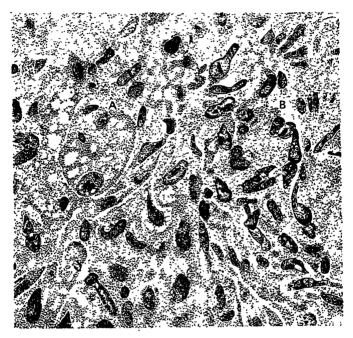


Fig. 86.—Early lepromatous lesion, showing large foamy cell (A) in the deeper tissues and a leprotic giant cell (B). The main cells are epithelioid in type. (After Cochrane.)

The suggestion has been made that this test may be employed in non-leprous subjects as an index to resistance to leprosy. Applying it to non-leprous children of leper parents, Rotberg found that positives increased with increasing age, reaching the maximum of 50 per cent. at the age of ten. This is taken to indicate that resistance is low in young children, but increases with age, but there is no evidence, as in tuberculosis, that resistance may be ultimately broken down by massive or repeated infections, whilst slight infective doses tend to raise resistance. Another indication of resistance is the abortive case, when slight, though definite, lesions appear and disappear without apparent cause. About the inheritance of acquired immunity there is still little clear knowledge.

In Burma leprosy is of a much more severe type in native Burmese than in Indians living in that country. Some authorities have claimed that

racial immunity is the result of prolonged and intimate contact with leprosy at some remote period of history and its disappearance as an endemic disease has been explained on this basis, but there is really little evidence to support this. It is more natural to explain the persistence of endemic leprosy in certain European countries, and its disappearance from others, on the basis of improved sanitation and hygiene than on racial immunity.

Localized immunity is observed in active lesions, especially those of the tuberculoid type. In the annular form of eruption the active inflammation spreads at the margins while the disease dies down at the centre, leaving only a slight discolouration, or perhaps a mild sensory impairment; or, again, a major tuberculoid lesion may flare up and die down again, leaving

only a slight visible scar to indicate its former site.

Probably the majority of humans are non-susceptible to leprosy save during the critical years of childhood and adolescence. Even when infection does take place there is a natural tendency to recover, so that the possibility of arrest in the initial stages has only been realized in recent years. Cochrane has shown that in children more than 50 per cent. of all neural lesions show improvement over a period of three years; possibly this is related to the lepromin reaction, as the great majority give a positive result.

Clinical features.—Primary infection.—The early manifestations of leprosy may be vague and indefinite, such as malaise, weariness and mental depression. The probability is that bacilli reach the corium of the skin. or mucosa of the nose, mouth or pharynx, through some breach of the epithelium. It is difficult to be certain whether the primary lesion is the initial one, or some metastatic manifestation but, when several appear on widely-separated parts of the body at the same time, they naturally represent secondary lesions derived from some primary focus. Rogers stressed the following points as worthy of notice: in hilly and stony districts in India the primary lesions are most commonly observed on the feet. The first lesions on the body are scattered most densely on the extensor surfaces, especially on those parts exposed to pressure when lying down, such as the cheeks, outer surfaces of the shoulders, arms, buttocks and outer surfaces of the thigh. The flexor surfaces, on the other hand, are remarkably exempt. The affected parts are just those most exposed to insect bites and to the excoriation by the nails in attempt to allay irritation.

The fact that leprosy is more prevalent in hot, moist climates may to some extent be explained by the greater softness and moisture of the skin and the frequency of prickly heat. In cold climates, when the body is protected by clothes, it appears that a larger proportion are inoculated through the nasal mucosa. The face around the nose is a frequent site of *leprides* which are devoid of lepra bacilli; the nasal mucosa is frequently involved and is probably the immediate site from which the leprides arise.

Incubation period.—This is undoubtedly very variable and may be very prolonged: as long as 6 to 8 years. In South Africa the average period impodular cases is about 2 years though it would be fair to state that the

general average is $3\frac{1}{2}$ years, the extremes lying between $5\frac{1}{2}$ months and 4 years. It may well be that very long incubation periods may represent long latent periods after infection and before outward visible signs become apparent. Early discoloured anæsthetic patches may be overlooked for years.

In children of lepers living with their parents in the Culion Island colony in the Philippines it was observed that the disease developed in 22 children within 4 months to 4 years from the time of their removal from the source of infection. Certainly in one case it took place during the first year of life. Muir has recorded a case in a three months' old child. There appears to be direct relationship between closeness of contact with the diseased and the early development of symptoms. The length of incubation is considerably affected by the general health and habits of the patient, as well as by the climate. The first signs of leprosy may appear during the course of some other disease, such as dysentery, enteric fever, malaria or influenza.

As compared with tuberculosis, one of the chief characteristics of leprosy is the absence of toxicity; enormous numbers of bacilli may be present in the body with few signs. The local inflammatory reactions to lepra bacilli vary within wide limits. Thus, in one patient the disease is so localized that it affects one small skin area or the main nerve supply. There may be acute inflammatory swelling, local pain, trophic, sensory and other disturbances. Bacilli can be demonstrated with great difficulty. In contrast, a second case may show involvement almost of the whole body, so that a preparation taken from any part of the skin may reveal numerous bacilli, though the patient is not acutely ill and is able to be about and do his work. The nerves are not noticeably thickened, and superficially the skin appears normal. At any stage during invasion sudden exanthematous reactions may appear, accompanied by fever and general symptoms.

The chronic onset is so gradual and insidious that the disease has advanced to a considerable extent before any abnormality is evident. There may be tenderness, tingling or thickening of a nerve, an area of anæsthesia, perhaps with some change in the appearance of the skin, insensitiveness to burning, formication, tingling or numbness of extremities. Discoloured skin patches may be mistaken for eczema or ringworm; these may at first be small,

gradually increasing in size.

In the acute onset there are occasionally multiple lesions with less diffused margins, which tend to spread rapidly and which contain very numerous bacilli. The first noticeable sign may be an evanescent rash. The onset may be determined by some other acute disease, such as malaria or typhoid, which lowers the resistance. It may also be the sequel to chronic infection, such as syphilis, ancylostomiasis or chronic disease of the gastro-intestinal tract. The period of life may also have some bearing, e.g. extra strain imposed on the body during puberty, parturition and menopause.

Classification of leprosy.¹ Clinical types.—The somewhat complex classification adopted by the Cairo Congress in 1938 has been modified

¹ The reader should consult the Manual of Leprosy, by E. Muir (1948).

and simplified by that of Rio de Janeiro in 1946 on the basis of the actual degree of resistance of the tissues to the leprosy bacillus. Low resistance produces the definite histological picture of the leproma which appears in all tissues. High resistance produces a different picture known as tuberculoid. The first is the result of absence of tissue reaction; the second that of effective reaction, but there is a pre-lepromatous and a pretuberculoid incubation period in which the reaction to the bacilli is slight. The affected tissues during this period show changes which do not indicate the type which may eventually evolve and this form is known as Uncharacteristic. The main types are, therefore, Lepromatous, Tuberculoid and Uncharacteristic.

The following is the clinical sub-classification:—

TypeSub-groups Lepromatous Macular. Infiltrative (diffuse). Nodular. Neural. Generalized. Uncharacteristic . Macular. Neural. Neuro-macular. Tuberculoid . Macular. Papular. Neural. Maculo-neural.

Lepromatous type.—This is the severe type. Owing to the low resistance of the patient the tissues form a fertile soil, so that the disease may advance before it is recognized. When reaction takes place widespread skin lesions appear. When once established lepromatous leprosy may be divided into four stages:—

Reactionary.

- (a) Macular, the lesions of which may be circular or elliptic, showing pink in a light skin, pale or coppery in a dark, with slight loss of sensation.
- (b) Diffuse or infiltrative. The macules join together to form larger areas of diffuse infiltration.
- (c) Nodular. There is a tendency for irregular thickenings to protrude in the form of nodules or localized broader patches on the forearms, legs, face and ears, producing leontiasis of the face.

(d) Ulceration or resolution may accompany acute exacerbations. Sometimes resolution takes place without ulceration.

The typical cell reaction of this type is a lepra cell with vacuolated appearance or the foamy cell (Fig. 86).

Bacillæmia is common in advanced cases, especially during exacerbations. The lepra reaction (p. 580) is common in the lepromatous form.

Tuberculoid type.—This is the mild type of leprosy. Sometimes there is only one lesion and that may occur on what was the site of inoculation. The term "tuberculoid" is used on account of the histological resemblance of this type to chronic lesions in tuberculosis.

The clinical course depends upon the degree of resistance. Some lesions are actually abortive. There are also leprides. The characteristic clinical feature is the "tubercle" about the size of a pin's head slightly raised above the surface of the skin and generally darker in colour. The typical lepride consists of three zones, a tessellated margin of tubercles, an intermediate hyperchromic area of coalesced tubercles and a flattened atrophic centre paler than the normal skin. Some leprides have them; others have broader red margins. Mucous membranes are little affected.

Tuberculoid skin lesions present sensory changes in tactile pain and thermal sensation; there is deformity or loss of hair, dryness of skin and suppression of sweat. Nerve lesions are much more marked. In typical cases in the histological picture the epithelioid cell takes the place of the lepra cell and bacilli may be absent or inconspicuous. In general the "lepra" reaction is much less severe in the tuberculoid type.

The Uncharacteristic type.—This includes many cases which cannot be placed under the above-mentioned types. The early cases may show one or more patches on the skin, the margin of which is not raised or clear cut. Tissue reaction is slight.

Polyneuritic lesions.—Involvement of peripheral nerve trunks produces sensory changes in the extremities, which commence distally and spread in a proximal direction. They result in trophic changes, such as anhidrosis, glossy skin, keratosis, perforating ulcers, atrophy, necrosis of bones and mutilations of the extremities.

Lesions of peripheral nerves.—Thickening of nerve trunks is common. The ulnar nerve is commonly affected at the elbow, and the radial at the wrist. The auricular and the superficial peroneal (at the ankle) nerves can often be distinguished as cords under the skin, as well as the medial cutaneous and the crural branch of the internal popliteal in the calf. Thickening of the branches is generally correlated with leprides.

Leprous nerve abscess is not uncommon in India associated with the neural type, or with injury. It occurs in superficial nerves—usually the ulnar, median cutaneous of forearm, great auricular or crural. The abscess is usually central and spindle-shaped and contains pus similar to that of glandular tuberculosis. Lepra bacilli may be present.

Anidrosis, preceded by hyperhidrosis, may be one of the first noticeable signs.

Hypopigmentation, usually noticed in highly pigmented skins is not

usually complete, as in leucoderma, but partial.

Hyperæsthesia, with an area of the lesion tender to touch and painful stimuli, precedes anæsthesia.

Anasthesia. At first it consists of loss of epicritic and then of protopathic sensibility.

Parakeratosis is recognized clinically by changes in the horny layer of the skin which becomes shiny and scaly.

Hyperkeratosis is best seen on the palms of the hands, or soles of the feet, and in the latter situation perforating ulcers usually form.

Hair and nails.—The hair follicles are affected; the hairs become soft and thick, breaking off at their point of emergence. The broken end

becomes club-shaped, but growth continues inside. Similar changes take place in the nails, which become thickened and curved and claw-shaped.

Vascular changes produce congestion and erythema, usually surrounding

the margins of the lesion.

Resistance is the determining factor whether the type becomes tuberculoid or lepromatous; the latter invariably shows greater concentration of bacilli in both nerves and skin. The lepromatous lesions are in the main symmetrical. Leprides and anæsthetic patches of the neural type are less so. When they cover large areas it is the result of gradually

extending lesions from comparatively small foci.

The "lepra" reaction is acute in onset and course, accompanied by severe, febrile constitutional symptoms when all the lesions suddenly become swollen and inflamed. It seldom occurs before the infection has become generalized and fairly far advanced. At the same time fresh nodules or macules, surrounded by ædema, appear, and cutaneous or subcutaneous nodules become pustular, break down and discharge pus full of Myco. lepræ, many of which are diphtheroid in shape and staining reactions. As the reaction subsides, the lesions remain covered with desquamating epithelium. This reaction may last a few days, or may be prolonged for weeks or months. It may remain confined to the face or extend to the whole of the body. The factors which determine its onset are not so easily ascertained.

Intercurrent disease, such as malaria, may light up the lepra reaction and, moreover, in the lepromatous form, small doses of potassium iodide may produce a similar condition, but these symptoms usually rapidly fade with elimination of the drug from the body. In India there seems to be a predisposition to the lepra reaction, which is much less common in Central Africa. In the neural type the reaction differs, as the tuberculoid form of lesion is more limited, so the febrile and toxic symptoms are less severe.

In both the main forms of leprosy the reaction represents an attempt to destroy the causative bacilli. In the minor tuberculoid form this is often successful when bacilli are scanty, but in the major tuberculoid, where they are more numerous, it is not. In the lepromatous form the reaction is less severe when there are masses of bacilli to be destroyed and so, as the result of toxic absorption, the patient's resistance is reduced and the lesions become even more widespread than before.

The process spreads to the nerve-trunks and ramifications. The nerves become swollen, congested and tender, and there are neuralgic pains. Blisters and bulke may be formed, with ultimate sloughing, which may even proceed to bone necrosis. Perforating ulcers in the feet are frequently the result of nerve reaction in the lower limbs. Herpes zoster may accompany involvement of the intercostal nerves. Minor reactions cause only minor inflammatory swellings of the lesions and the appearance of new ones. Ryrie has found that the onset of the lepra reaction is heralded by hyperalgesia of the soles of the feet.

Distribution of leprous lesions.—Those parts of the body most exposed appear to suffer early. In Europeans these are the hands and face. In natives exposed to injury the feet are most liable.

Head and neck.—The ears are more constantly affected than any other part, and in a suspected case it is always as well to look first at the auricles, where any thickening of the lobule may be readily detected by palpation with finger and thumb. Nodular lesions are seldom seen on the palms of the hands or soles of the feet and are exceptional on the penis and scrotum. The scalp was formerly said to be seldom affected; this is partly due to its anatomical structure, and partly to the fact that it is hidden by hair, but, as a matter of fact, leprous alopecia is by no means uncommon. In the neck the cutaneous branches of the nerves are early involved, especially the great auricular, which may stand out on the skin and be quite conspicuous.

Palpation of this nerve may be a great help in early diagnosis.

Initial lesions of all types are common on the face, especially on the forehead. There is often loss of hair (madarosis) of the eyebrow, especially the outer part, and of eyelashes, even in the early stage of the disease. Lesions of the nasal mucosa are often present, though they may pass unnoticed unless specially sought. They may cause nasal catarrh and often intermittent epistaxis. There may be merely a diffuse erythema, or erythematous patches, or general infiltration leading to corrugation of the skin. Nodular eruptions appear on the eyebrows, leading to leontiasis, and there is often a characteristic thickening of the nose. In the neural form anæsthetic patches appear, together with paresis or paralysis of groups of muscles, which create a peculiar mask-like expression (Fig. 87). When the orbicularis palpebrarum is affected the results are serious, as failure to close the eyes permits trauma of the cornea. Paresis of the sphincter muscles of the mouth leads to dribbling. The senses of taste and smell may either be much diminished or lost entirely. Pressure on the facial nerve frequently causes intractable facial paralysis.

Lesions of the eyeball may be divided into two categories: those due to the presence of Myco. lepræ in the eye, or those due to interference with the nerve supply. In the neural type there are no actual leprous lesions, but the seventh cranial nerve is frequently involved giving rise to lagophthalmos from myoatrophy of the orbicularis. The eye complications are then due to exposure and trauma. In the tuberculoid type the eyes are not involved, except when the lesions are situated around them when madarosis (loss of eyebrow and eyelash hairs) and conjunctival congestion result.

When Myco. lepræ is present in the eye, lesions are caused by spread either along the lymphatics or bloodstream, and Myco. lepræ has been found in the conjunctival secretion and in scrapings from the conjunctiva in clinically healthy eyes. Early ocular involvement can only be diagnosed by examination of the eye with the slit lamp and corneal microscope. Leprous nodules are never found on the conjunctiva, but it is infected by spread from the surrounding tissues. The disease may attack the cornea, which is the most vulnerable tissue; then a ground-glass pannus spreads inwards over the pupil from the corneal margin and may considerably interfere with vision. Leprotic nodules of the cornea are by no means uncommon and, when deeper, may bulge into the anterior chamber. The infiltration destroys Bowman's membrane and produces a sclerosing keratitis and even an anterior staphyloma. Interstitial keratitis is a degenerative circular keratitis extending round the entire corneal circumference. Again,

leprotic infiltration may spread from the sclera along the anterior ciliary vessels, setting up iridocyclitis. All the grave manifestations of iridocyclitis may be observed—posterior synechiæ with seclusion and occlusion of the pupil, secondary glaucoma, vitreous and lens opacities, hypotension, retinal detachment and atrophy of the eyeballs. In all varieties of iridocyclitis atrophy of the iris is present. The whole tissue becomes grey and dull, the crypts disappear, the blood vessels become visible and finally

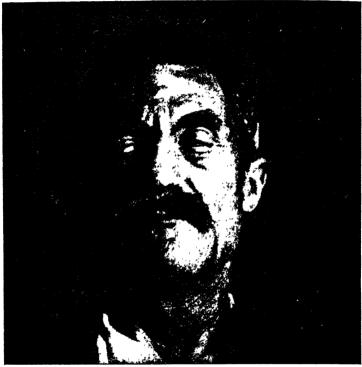


Fig. 87.—Leprotic infiltration causing paresis of facial muscles and paralysis of orbicularis palpebrarum.

holes make their appearance. When there are nodules of the iris the eye is doomed. In the posterior segment of the eye choroiditis has been observed occasionally before the anterior segment has been involved. Involvement of the optic nerves has been found an early and only sign of ocular leprosy (Kirwan). In Rogers's experience in India, from 5–10 per cent. of lepromatous cases develop disease of the eye or its adnexa. Madarosis occurs in lepromatous and also in the tuberculoid form, but not in the pure neural type, and it has been asserted that there is close correlation between the degree of madarosis and the gravity of the eye lesions. Lepromata occur on the margin and other parts of the upper eyelid, but are never found in the lower.

In neural cases the eve is often involved. Lagophthalmos gives a pathognomonic expression to the eye and is due to progressive myopathy of the orbicularis oculi which may be uni- or bilateral and is generally preceded by twitching of the eyelids. The palpebral fissure becomes wider in proportion to the progressive weakness of the orbicularis oculi. Anæsthesia of the cornea and the deposition of fibrous laminæ, together with paralysis of the palpebral muscles, abolish the corneal reflex and prevent normal closing of the eye by day or night, so that progressive ulceration of the cornea takes place, and general panophthalmitis may Ectropion leads to eversion of the punctum lachrymale and discharge of tears, with eventual destruction of the lacrymal sac. Claude-Bernard-Horner syndrome is characterized by ptosis, enophthalmos, myosis and varied pigmentation of iris (heterochromia), unilateral anidroses and lowered ocular tension. Pinching of the skin of the neck fails to cause dilatation of the pupil. The eve symptoms are not affected by instillation of cocaine.

The nose.—The habit of "picking" the nose, especially in children, probably plays a part in lesions of the mucosa, and those parts of the nasal septum and inferior turbinates within reach of the fingers are most commonly affected. All degrees and types of infection which occur in the skin are found in the nasal mucosa; nodules may be present on the turbinates, ulcers and scars on the septum. Perforation of the septum and deformity of the nose may result. When there is ulceration, the discharge contains large numbers of Myco. lepræ, so that these cases constitute a serious source of infection to others.

Mouth, pharynx and air passages.—Lesions of the lips are sometimes found as an extension from the face. Nodules appear at the outer margins of the lips, and fibrous constriction may cause partial stenosis. Nodules of the tongue are seen in advanced cases. The palate may be affected by diffuse or nodular lesions. Perforation of the palate may occur in the absence of syphilis. The larynx is not primarily affected, but may be involved by extension; the onset is usually insidious. In some lepromatous leprosy the soft palate, uvula and ary-epiglottic folds are swollen and indurated; tubercles of various sizes may appear. Later there is ulceration; constriction of the glottis may necessitate tracheotomy. Fibrous constriction is the cause of the hard whispering voice of the confirmed leper, giving rise to the brassy leprous cough. In primary nerve leprosy the throat is seldom affected. Lesions of the pharynx and tongue are exaggerated during the reactionary phase.

Upper extremities.—Primary lesions are not uncommon; in those who wear European dress they tend to be limited to the hands. The flexor surfaces tend to be much less affected than the extensor, possibly because they are more liable to injury.

Skin and nails.—The nails are not usually affected in the early stages. In the lepromatous type the most marked changes occur when there is deep infiltration of the skin of the fingers. The nail becomes attenuated and there is longitudinal ridging of the nail-bed. In the nutritional

lesions of the neural type the nail is thickened and tends to split transversely. Trophic blebs and blisters on the hands are frequently the result of burns and bruises to which the anæsthesia exposes them.

Muscles.—Muscular atrophies are most conspicuous in neural types, chiefly from involvement of the ulnar nerve. Thus, the intrinsic muscles of the hands are affected, with flattening of the thenar and hypothenar

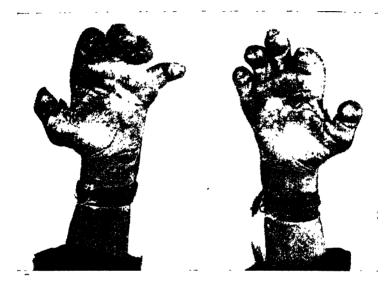


Fig. 88.—Nerve leprosy: main-en-griffe. (Dr. H. K. Giffen.)

eminences so characteristic of ulnar palsy. The characteristic main-engriffe is a later development, with hyperextension of the metacarpophalangeal and flexion of the interphalangeal joints. The whole deformed hand becomes rigid, as if carved out of wood. Finally, with overgrowth of the nails and progressive osteoporotic changes in the phalanges, it becomes the typical leprous claw hand, like some deformed vulture's talon. Wrist drop may develop, chiefly from disuse; as the bones shorten, a claw-like nail may often be implanted into a metacarpal. There is seldom any affection of the upper arm (Fig. 88).

Bones.—Decalcification and osteoporosis of the bones accompany the neural form. The phalanges become atrophied, and may actually become absorbed without sepsis or open wound. The metacarpals are less often affected. The process is often complicated by sepsis, and consequently necrosis of bone (Fig. 89).

Lymph glands.—In skin leprosy there may be enlargement of the axillary or inguinal glands. This may be due either to invasion of Myco. lepræ or septic organisms.

Lower extremities.—Initial lesions in natives commonly occur on the feet, and a patient may suffer from the more chronic types without noticing much amiss. Often the first sign noted is a bleb or blister. The superficial peroneal nerve, as it passes round the head of the fibula, is specially affected and is felt as a thickened and palpable cord. Drop-foot resulting from peroneal paralysis is not uncommon. The posterior tibial nerve

frequently inpretibial volved. \mathbf{The} skin is stretched, shiny and hairless; it does not sweat but usually becomes excessively dry and cracked. In others. again, there is elephantoid swelling of the feet extending to the knees. with depigmented anæsthetic patches, hornv hyperkeratosis and mutilation of the toes.

Perforating ulcers of the soles of the feet are painful and crippling; they are associated chiefly with neural cases and are the direct result of nerve, involvement. The epithelium of the sole becomes thickened and inelastic. This leads to fissuring of the skin and



Fig. 89.—Late effects of nerve-leprosy of 22 years' duration. (Dr. H. K. Giffen.)

the formation of ulcers. The feet become flattened and painful, owing to destruction of the musculature of the arch, and the anæsthesia may permit many injuries. Trophic changes in the muscles and periosteum lead to decalcification and absorption of the bone, which may be even more extensive in the foot than in the hand. Thus, the astragalus is often completely absorbed. Sepsis through cracks and abrasions is a terminal event. Nodules on the legs are most frequently found at the sites of injury or friction. They are especially common on the internal and external malleoli. Lymphangitis in the lower limbs is not uncommon.

Body and internal organs.—Lesions on the trunk do not differ in any essentials from those on the extremities. The middle line is less affected as a rule. Lesions on the front of the chest are said to be comparatively rare. In nerve leprosy typical herpetic lesions containing Myco. leproc have been reported. Induration and even hypertrophy of the nipples are very common in the reactive stage, followed by retraction in the phase of resolution. It is said in India that, when the lower abdomen is protected by a loin cloth, lesions of the abdomen are confined to the upper half.

Lesions of lungs have not been recorded. Large quantities of purulent

sputum are due to bursting and discharge from nodules in the trachea and upper bronchi. Pulmonary tuberculosis not infrequently complicates the more severe forms of leprosy. Lepra bacilli are commonly found in spleen and liver, but do not seem to give rise to any special symptoms.

Genital organs.—Testicles are affected in advanced cases. Sterility is more common in males than in females, and it is rare for the ovaries to be involved. Swelling of the male breast (gynæcomastia) commonly occurs in cases in which the testes have been destroyed. (Fig. 90.) The birth-rate amongst lepers appears to depend on the fertility of the male.

Lymphatic glands are enlarged in the vicinity of gross infections of a

part, especially in the neck, axillæ and groin.

Resolution.—Leprous lesions may resolve spontaneously. Major tuberculoids may disappear, with deposition of scar tissue. Minor tuberculoids often heal up at the centre, with little change in the texture of the skin. In the lepromatous type, nodules which resolve leave flat scars like deep burns.

Incidence.—Leprosy is more common in men and assumes a more severe form. In Norway the few remaining cases are chiefly in females, which is explained by their greater longevity and the milder character of their disease. Before the age of puberty children of both sexes are almost equally affected. The periods of puberty and childbirth impose a severe strain and increase somewhat the incidence in the female. The chief factor in the considerable excess of male cases is the greater freedom they enjoy. As in tuberculosis, the majority of cases are infected during the first two decades, and probably few contract the disease after 40.

Little is known about the factors of race, susceptibility and resistance. Differences which have been observed are probably explicable on climatic, social, dietetic and economic grounds. In India and Africa leprosy is especially common and severe in races with mixed European blood. That the social condition has a marked influence on the incidence and severity of leprosy is self-evident. In Norway it was formerly confined to fisherfolk living under very primitive conditions, but in India wealthy and highly-placed people are quite commonly infected. Rogers is of the opinion that in these it is a result of bed-infection.

Duration.—When leprosy is acute and febrile it may be fatal within two or three years, but in the great majority the course of the disease is very slow.

Diagnosis.—Early diagnosis is of the utmost importance, but many factors militate against it. It is, of course, easy to diagnose obvious and advanced cases. The ignorance of the patient, his dread of the disease, and the fear and superstitions of the general public may hinder prompt recognition. The earlier indications are the discoloured patches on the skin, and symptoms referable to involvement of the peripheral nerves, such as tingling or numbness, formication, or a feeling of woodenness in the limbs. In the majority of cases the first lesions noted are depigmented anæsthetic patches. Of fundamental importance are impairment of sensation, thickening and tenderness of nerves and demonstration of acid-fast bacilli. To test sensation, the patient should be stripped and blindfolded. For



Fig. 90.—Leprosy, showing hypertrophied nipples (gynæcomastia).

testing anæsthesia to light touch, a feather should be used; analgesia is tested by pin-prick, using an area of normal skin as control. The two-pin test is often positive when the feather test is negative. Loss of thermal anæsthesia is important. Hyperæsthesia and paræsthesia may precede anæsthesia to light touch. Tuberculoid lesions are usually more insensitive

than lepromatous.

Thickened nerves may be felt on palpation, and tenderness elicited by striking an area sharply with the finger or patellar hammer. The ulnar nerve is commonly affected above the elbow: the superficial peroneal at the head of the fibula behind the knee; the radial as it curves round the humerus, or its branches as they pass over the lower end of the radius; the posterior tibial below the inner malleolus; the great auricular as it runs parallel to the external jugular vein; and the branches of any particular nerve supplying a tuberculoid lesion. Examination of a smear for Myco. lepræ, by cutting down on the epineurium of a nerve, may occasionally be necessary.

Bacteriological examination.—In tuberculoid macules bacilli are difficult to find, and should be sought at the margins. In the lepromatous form, where there are no outstanding nodules, the lobule of the ear is the site of choice. Lymphatic gland puncture, as well as the examination of blister fluid by carbon dioxide snow, may be useful.

Biopsy of the skin may be made by smears made from a "snip" or by section. The scraped incision method of Wade consists of pinching-up the skin and applying compression to stop bleeding. With a small scalpel a cut 5 mm. long is made well into the infiltrated layer. All blood should be wiped away and, with the blade transverse to the incision line, the side and bottom of the cut should be scraped repeatedly, and the material spread on a slide and examined. The selection of the site is important, though failure to find bacilli in one smear does not justify a negative diagnosis. In all doubtful cases skin sections should be examined. Formalin should not be used as a fixative as it interferes with the acid-fastness of the bacilli. Zenker's fluid or alcohol are preferable.

Examination of the nasal mucosa is as important as that of the skin, and frequently a positive result is obtained when the skin is negative. A sharp-pointed tenotomy knife is the best instrument, and material should be sought in the septum and inferior turbinate. If there is ulceration, slight scraping suffices. Otherwise, a small piece of mucous membrane should be scraped off. Cotton swabs should not be used, as they frequently harbour saprophytic acid-fast organisms which may be mistaken for Myco. lepræ. The standard Ziehl-Neelsen method should be used for staining. De Souza-Araujo utilizes his method of clamping the skin until ischæmic and then puncturing it in order to obtain lymph for staining in search of leprosy bacilli. A special method is that of Hallberg with Nachtblau, as for tubercle bacilli, which is specially useful for sections of suspected skin lesions.

In the tuberculoid form bacilli are scanty, but then with typical lesions and epithelioid and round-cell infiltrations and a few giant cells differentiation from cutaneous tuberculosis is not always easy. No caseation is ever visible in leprosy sections. There may be peripheral neuritis with surrounding round-cell reaction.

Sternal puncture is often positive and is considered by Lowe to be of equal value to skin biopsy. The morphology of the bacilli differs according to the activity of the case. In lepra reaction they appear more granular and diphtheroid. Castro's method (1947), has been found to show more bacilli than the ordinary methods, especially when they are few and also shows up the appearance of beading. The solutions required are (a) carbol fuschsin, (b) 10 per cent. solution of potassium phosphate, (c) hydrochloric acid 3 ml., ethyl alcohol (96 per cent.) 97 ml., (d) methylene blue 1 grm. With 1,000 ml. add 10 ml. of (a) five drops of (b). Flood the slide with stain and steam for 5 mins. Pour the solution off the slide and decolourize with (c). Counterstain with (d) for one minute.

Rubino's reaction.—The blood sedimentation rate is constantly increased in leprosy and, concurrently, the cholesterol content of the blood is reduced (Westergren's method with citrated blood). Rubino has

advocated an agglutination-sedimentation test with formolized sheep's corpuscles. The serum is said to contain a specific substance which causes rapid agglutination and sedimentation of these corpuscles. It is claimed that the reaction is specific and sedimentation is produced in less than one hour.

The lepromin reaction (Mitsuda).—Clinically and histologically it resembles the Mantoux reaction in tuberculosis, but it may not become apparent for several days (p. 575). Cochrane found the lepromin reaction positive in 60 per cent. of neural and 100 per cent. of tuberculoid cases. The lepromatous type gives a uniformly negative reading as it is an allergic response. Some healthy children give false positive reactions. Possibly lepromatous cases will alter from negative to positive after prolonged sulphone treatment.

Technique of the lepromin test.—Material is obtained by removing large, soft, nodules which are boiled in water for 20 minutes and divided into fine fragments with scissors. The epithelium is then removed and the material dried for a few hours with an electric fan, then in a vacuum desiccator over pure sulphuric acid. The dried material is ground up to a fine powder in a glass mortar and stored in a desiccator. In preparing the suspension 0.4 grm. of the dried powder is ground up with 10 ml. of saline and the fluid pipetted off, a process which is repeated three or four times. Carbolic acid (0.5 ml.) is then added and made up with normal saline. The suspension is made up in 1 ml. ampoules, sealed and heated at 120° C. for half an hour. Standardization is difficult. The active principle is protein of Myco.leprox. Dharmendra and Lowe have made a standard antigen from dried and partially defatted leprosy bacilli. (The dose is 0.1 ml.) The antigen should be kept in sealed glass ampoules.

A series of intradermal tests with full strength lepromin are made in dilutions of 1 in 2, 1 in 4, 1 in 8. Stronger suspensions, as a rule, give stronger reactions. A standard smear is made and the number of bacilli estimated. The skin on the inner aspect of the arm is chosen, the customary dose being 0.2 ml. The injection must be made intradermally; a slight serous effusion follows it, but disappears after a few days. With Dharmendra antigen there is in positive cases an angry flush 6–12 mm. in diameter and soon a nodule appears at the site of inoculation between the first and third weeks, increasing in size up to a maximum. The degree of reaction is read by measuring its size by a sliding calliper. In strong reactions there may be slight necrosis. In healthy adults not infected with leprosy the nodule is 6–10 mm. but in resistant cases it is much larger. The lepromin reaction is of use as a means of testing natural resistance to leprous infection, the higher the reading the better the chances of recovery. Readings should be registered as -, +, + +, or + +.

The iodide test.—This test is of value in assessing the infectivity of cases when repeated bacteriological examinations of skin and nasal mucosa have given negative results. It should only be used, however, when the general health is good and when the blood sedimentation tests are within normal limits. A single dose of 2 grm. of potassium iodide in a glass of water is given at night. This may cause appearance of new cutaneous lesions or efflorescence of old ones, pain or tenderness of the nerves, pyrexia and increased sedimentation rate. The skin and nasal mucosa should then be examined for $Myco.\ lepræ$. If any reaction occurs, the next dose of potassium iodide should be delayed until it has subsided. If not, increasing doses of 4, 6, 8, 12, 16 grm. should be given at fourteen-day intervals, always with plenty of water. Should no further reaction occur, the leprotic infection may be regarded as arrested.

Subsidiary signs.—Anhidrosis, often preceded by hyperhidrosis, is characteristic of chronic cases, and is usually present in tuberculoid macules. In doubtful cases pilocarpine, 0.2 ml. of 1 in 1,000 solution, is injected intradermally in a suspected patch and a similar amount in adjacent healthy skin. Both areas are then painted with tincture of iodine and, when dry, powdered with starch. The control area sweats, turning the starch blue. Absence of sweat at the point of injection

indicates leprosy.

A useful diagnostic aid is described by Arnold as the intradermal mecholyl test for anhidrosis. The action of mecholyl chloride (almost identical with acetylcholine) is similar to that of pilocarpine. Denervation of sweat glands by leprous neuritis is the cause of anhidrosis, usually affecting the most distal portions of the post-ganglionic nerve fibres. In carrying out the test, equal areas of leprous and healthy skin are painted with a solution of castor oil, iodine and absolute alcohol. Then 0·05-0·1 ml. aqueous solution of mecholyl chloride are injected intradermally at the border of the lesion so as to produce a wheal. The whole area is lightly dusted with powdered starch as an atomizer. Within a few minutes sweat droplets appear on the functionally intact skin, which becomes black from the iodine and starch combination. The response is negative when no sweat drops appear within the area tested.

The histamine test of Rodriguez is somewhat similar in slight or early cases. A drop of 1 in 1,000 solution of histamine is placed within the margin of the suspected area, and a second outside. A prick is made with a needle

through the drop. A red flare appears in normal skin.

Parakeratosis, hyperkeratosis, ichthyosis and alopecia.—The first three conditions are interconnected and are due to malnutrition followed by changes in the stratum corneum. The surface of the skin is shiny with scales. Hyperkeratosis is best seen on the palms of the hands and soles of the feet, where the epithelium becomes abnormally thick and is apt to split, forming a superficial perforating ulcer. Somewhat similar changes take place in the nails, whilst loss of hair in the beard, eyebrow area and scalp are well known.

Differential diagnosis.—The characteristic marks of leprosy are sufficiently distinctive, but they have to be differentiated from psoriasis, seborrhoeal dermatitis, various forms of tinea, eczema, lichen ruber planus, pellagra and filarial disease. Blastomycosis produces skin lesions reminiscent of leprosy. From syphilis and yaws, however, it may not always be so easy. Syphilitic and yaws skin lesions may often closely resemble the maculæ of leprosy, but the absence of sensory changes and reaction to treatment are sufficiently distinctive. The Wassermann reaction alone cannot always be depended upon in differential diagnosis as syphilis and leprosy frequently co-exist. In mild early cases of leprosy positive reactions denote coincident spirochætal infection, but in advanced cutaneous and neural cases, especially those subject to lepra fever, a positive reaction does not necessarily always indicate a syphilitic infection. Lloyd, Muir and Mitra reported that 68 per cent. of nodular and 27 per cent. of neural cases in adults gave positive reactions.

The thickened skin of crab yaws on the feet may roughly resemble leprotic hyperkeratosis and may give a semblance of anæsthesia. Gangosa

of vaws may be mistaken for nasal leprosy.

The early lesions of mycosis fungoides might possibly be mistaken for early nodular leprosy, and leucoderma is not infrequently associated with leprosy in the popular mind. It is extremely common, especially in India, and in negro races, and unfortunate sufferers are sometimes to be found in leper asylums. Depigmentation in leucoderma, however, is more complete and sensory changes are absent. Lupus vulgaris and other tuberculides are very likely to be mistaken for leprides, and in both diseases acid-fast bacilli are difficult to demonstrate. Lupus evinces a greater tendency to scar formation and there are no sensory changes.

Cutaneous leishmaniasis and, in South America, espundia, may be mistaken for leprosy. The lesions on the skin of the face tend to concentrate round the mouth and nose and form a more raised margin than those in leprosy. Demonstration of the Leishman-Donovan body will always settle the matter, but leishmanial lupus-like lesions on the ears may cause difficulty (see p. 168). Acrodynia, burns and other injuries may leave behind anæsthetic scars. Eunuchism has been mistaken for leprosy on account of the absence of eyebrows and the smooth, shiny appearance of the skin.

Neural leprosy has to be differentiated from syringomyelia, in which analgesia and loss of heat sense are accompanied by retention of sense of touch and normal sweat function. The absence of nerve swelling and tenderness is important. The nerve injuries caused by trauma of the ulnar nerve or by cervical rib may possibly be called into question, but can be settled by X-ray examination. Bernhardt's syndrome, or neuritis of the lateral femoral nerve, may cause anæsthesia of the antero-lateral region of the thigh. Raynaud's disease has been confused because of trophic changes; hypertrophic interstitial neuritis (Dejerine-Sotta's disease) may cause confusion; this is a rare condition with thickening of nerves which may be so great as to render them conspicuous, and is accompanied by sensory and trophic changes, as in neural leprosy, and ultimate production of claw hand. Von Recklinghausen's disease (neurofibromata) may sometimes resemble leprosy. Scarring and anæsthesia caused by extensive herpes zoster on the chest may give rise to difficulty.

Prognosis.—Leprosy may sometimes be a slight passing ailment, or may become the most repulsive loathsome disease known to man. The two important factors are concentration and distribution of bacilli in the body and resistance. Prognosis is more favourable in the neural than in the lepromatous type. The maintenance of a high standard of general health constitutes a most important element in prognosis. Some patients, even with advanced nodular lesions, are known to have partially recovered. On the whole, the earlier a patient comes under treatment the more favourable the prognosis. On account of the ease with which improvement in muscular power and in sensation can be determined, it is usually easier to assess the progress of the neural than of the lepromatous type. Very spectacular changes are most often seen in patients with tuberculoid lesions.

The danger of contact.—The factors which predispose to the danger of contact are closeness and duration, the infectivity of the case, combined

with the age and general health of the person exposed to contagion. A child may acquire the disease after even slight contact.

Recovery.—In early neural cases progress may be stayed or arrested with little or no deformity. But there is no acid test of absolute recovery, and it is said that in such an arrested case, some severe intercurrent disease may herald return of leprosy. From the patient's viewpoint the main thing is whether there will be permanent deformity.

Causes of death.—Leprosy differs from tuberculosis in its low mortality. As a rule the victims do not die of leprosy so much as from intercurrent disease. They die from complications or as the result of crippling deformities. Death may be due to asphyxia from obstruction of the larynx or trachea, or to prolonged lepra fever.

TREATMENT

Sulphone treatment of leprosy.—A number of sulphone drugs have been applied to the treatment of leprosy in recent years. In some instances, it is readily understood, that any final decision upon their value has to be postponed for some time. In 1942, hard upon the successful results obtained with Promin in tubercular guinea-pigs by Feldman. Faget was stimulated to try out this drug in leprosy. At first it was found to be too toxic by the mouth in the doses then advocated, but that it was well tolerated, up to 5 grm. daily, by the intravenous route in experiments conducted at the National Leprosarium, Carville, Louisiana. The parent substance is one of the sulphonamide group—and is known as D.D.S., D.A.D.P.S. or diaminodiphenyl sulphone (Fromm and Wiltman, 1908). As this drug was at first considered to be too toxic for routine administration, a number of derivatives have been prepared from it, but as Muir has stated (1952) in a recent paper there are now good reasons for believing that the nucleus, or parent substance (D.D.S.), is more effective in treatment than the others. It has been found that the effect of these disubstituted derivatives is largely dependent on their instability, and the D.D.S. that they liberate both before and after absorption. In this respect the derivatives should be regarded as uneconomical vehicles for giving D.D.S., as it is uncertain what amount is liberated and what is absorbed and, moreover, these complex derivatives are much more expensive to produce.

It has been found that during the first three months of treatment most complications are apt to occur, and it is wise to commence with the minimum effective dose of one 100 mgm. tablet twice a week. If no complications should ensue, this twice-weekly dose may be increased by one tablet every month till at the end of the third the patient is taking four tablets twice a week. The average leprosy case can tolerate this amount indefinitely. Some cases improve rapidly: others slowly. There does not seem to be any general rule. Cochrane gives bigger doses. He thinks that a dosage of 200–300 mgm. of D.D.S. twice weekly, or 1–2 ml. of a 50 per cent. aqueous solution can be tolerated.

Muir thinks that the safest criterion of improvement is the bacillary index (B.I.) which concerns the concentration of leprosy bacilli taken from the nasal mucosa and other parts of the body where bacilli are found in the greatest numbers.

Leprosy is benefited at all stages by D.D.S. treatment. but progress is more favourable the earlier the treatment is begun. In the later stages the patient becomes allergic to the lepra bacillus. Lepra reaction is the most distressing complication. There is considerable evidence that pains in the bones are due to inflammation in the cancellous tissue. In this D.D.S. in minute doses has a marvellous power in relieving the lepra reaction. In most cases initial D.D.S. treatment is accompanied by the appearance of rose-coloured fugitive nodules.

The following derivatives of D.D.S. have been prepared and have been

used in treatment:-

Promin (Feldman, 1940).—N-N didextrose sulphonate (D.D.S. content of 31.8 per cent.).

(2) Sulphetrone (1936).—Cinnamaldehyde bisulphite derivative of D.D.S. (D.D.S. content of 27.8 per cent.).

(8) Diasone (1938).—Formaldehyde sulphoxylate derivative of D.D.S. (D.D.S. content of 55.4 per cent.).

(4) Promizole.—Thiazole derivative of D.D.S. in which, in place of a benzine ring, a thiazole group has been inserted (D.D.S. content of 97.59 per cent.).

(5) Promacetin.—Acetyl sulphonamide derivative of D.D.S. (D.D.S.

content of 63.6 per cent.).

(6) Sulphone Cilag.—Mon-acetyl ester of D.D.S. (D.D.S. content of 75.7 per cent.).

The remark made about D.D.S. applies to all these derivatives, especially *Promin*. The dose advocated is 100 mgm. per day for two weeks: 200 mgm. per day for the next two weeks (=a blood level of 1 mgm. per 100 ml.): 300 mgm. per day from the fifth week onwards.

To counteract any consequent anæmia the patient should be given 0.7 gr. of ferrous sulphate daily, as well as liver, yeast and marmite. Muir now recommends injection of vitamin B₁₂ (Cytamen) and also A.C.T.H. (Roche, 1951).

Toxic effects are nausea, vomiting, hepatic pain and jaundice. Beneficial results are seen in the gradual shrinkage of nodules and the healing of lepromatous ulcerations in the skin and mucous membranes.

In the lepromatous cases, especially, there is improvement in vigour and sense of well-being, a diminution in the number of bacilli in the lesions, but febrile reactions may occur. In the tuberculoid form there are focal changes in the skin lesions, the activity of which usually subsides completely within six months. The inflammation of the nerve trunks takes a great deal longer to subside, but there is a concurrent and distinct improvement in the thickening of the nerves. Toxic reactions are first febrile and produce an eruption resembling erythema nodosum which has been appropriately termed "erythema nodosum leprosum" (Woolcott, 1947). This reaction is allergic in nature and is allied to the Herxheimer reaction.

More serious is a drug dermatitis which may proceed to exfoliation between the third and fifth weeks of treatment. In these cases the drug must be immediately discontinued for at least two months and antihistamine drugs (e.g. Anthisan) given immediately. Treatment can then only be resumed when the patient has been desensitized with repeated small and increasing

doses (e.g. 2 mgm. or less daily by injection).

The associated blood changes in sulphone treatments declare themselves as a decrease in the red blood-corpuscles with a corresponding decrease in the hæmoglobin values. With oral sulphetrone and diasone, especially. the anemia may be very serious indeed, but this does not occur, so it is claimed, when sulphetrone is given intravenously. When the hæmoglobin level has fallen below 12 grm. per cent. hæmatinics should be administered. but if below 10 grm., yeast should be given and the drug stopped. The more serious toxic signs are nausea, vomiting, jaundice and confusional mental states. The urine should always be tested for an excess of The most distressing disturbances are peripheral neuritis and severe ataxy. With diasone and sulphetrone gastric disturbances may occur. Rodriguez, in the treatment of 92 lepers during a period of six months to three years with promin, recorded that improvement had taken place in 81 per cent. Lowe remarks that sulphones exert little beneficial effect on trophic lesions caused by destruction of nerves. In normal doses in lepromatous cases definite response is noted within one month.

Thiacetazone (1950) Behnisch (thiosemicarbazone-TB₁), which has no relationship chemically to sulphone or sulphonamides, appears to be free from the side-effects which beset the action of the D.D.S. group. Ryrie (1950) claimed that thiacetazone had a more rapid action than the sulphones, though its action is similar. As there is evidence that it is an effective agent in the treatment of tuberculosis it should be tried out in those cases which show an intolerance to D.D.S., especially those which develop a drug dermatitis. The dose is 25 mgm. daily, increasing each week by 25 mgm. until 150 mgm. is reached. (Schneider and others give larger doses, 100–150 mgm. daily.) Children under twelve should receive half this dose. As a rule no anæmia is produced which is a great advantage. Its close relationship to iso-nicotinic acid, which exerts a specific action on

tuberculosis, is to be noted.

Para-aminosalicylic acid and streptomycin.—Although there is some evidence that P.A.S. and streptomycin have a similar action to that of the sulphones, their slowness and the necessity for frequent administration precludes their use in leprosy. Both drugs, especially P.A.S., may precipitate an acute exacerbation. Streptomycin is useful in suppressing ocular inflammation occurring during sulphone therapy and sometimes in improving cases in which progress has ceased.

The prophylactic value of these sulphone drugs is considerable as henceforward it will be possible to discharge patients from leprosaria after preliminary treatment to enable them to continue in their own homes.

The action of the sulphones.—The sulphones interfere with the metabolism of *M. lepræ*. When biopsies are done at various stages in sulphone therapy the organisms become reduced in numbers, especially in

the globi. These drugs apparently prepare the bacilli for more adequate phagocytosis and destruction of the macrophage cells. Clinical improvement in leprosy marches far ahead of the bacteriological. It may well be that the granular forms of the bacilli, which become evident during treatment, represent the resistant forms of M. lepræ. The bacilli under the microscope have the appearance of fragmentation. granulation and reduction to fine dust. Globi appear in the smears—some full of bacilli, others empty.

Improvement of the patient can be gauged in three stages: immediate, intermediate and delayed. In the first two the signs of progress are chiefly clinical. In the last stage estimation of bacilli in the skin has to be undertaken as follows:—

Five smears are taken from those parts of the skin where bacilli are present in greatest numbers. With a sharp-pointed knife, to incise to a depth of 2-3 mm., all five smears should be taken in serial order on one slide which should be fixed and stained with carbol fuchsii by the ordinary method. In gross infections the whole smear appears red and should be marked +5, when not so red and many globi can be seen, the mark is +4; but when there are few bacilli, no globi, and not more than one or two small clumps in the smear it should be +1. The other two intermediate counts are +2 and +3. To obtain the bacillary index (B.I.) the marks for five smears are added. The maximum B.I. is 25.

Chaulmoogra and hydnocarpus oils.—These remedies have for centuries been employed for leprosy in India and other countries. The oils are derived from the seeds of Taraktogenos kurzii, Hydnocarpus wightiana and H. anthelmintica. Formerly given by the mouth, or by inunction, the modern method is by injection. The oil is expressed from fresh, ripe seeds and when fresh is well tolerated. There is virtually no difference in the composition of chaulmoogra and hydnocarpus oils, though the latter has largely replaced the former. Hydnocarpus oil and its esters intramuscularly and intradermally are the most efficacious drugs, but the ethyl esters are more stable, but must be kept in hermetically sealed ampoules and used immediately. Esters must not be reheated.

Antileprol, ethyl ester of chaulmoogra, is dispensed in capsules of 1 grm., given intramuscularly, or by the mouth, twice weekly in increasing doses.

Alepol is sodium hydnocarpate, is soluble in water and is given in 3 per cent.

solution, intramuscularly, subcutaneously and intradermally.

Moogrol is a mixture of ethyl esters of chaulmoogra and is given in 1 ml. doses increased to 6 ml. at weekly intervals. The iodized ethyl esters, or iodized moogrol, are used for intradermal injection, by infiltrating the leprotic lesion and producing coalescing "injection wheals." These methods are employed at the present day as a means of reinforcing sulphone therapy, especially in reducing lepromata and indurated areas which do not respond readily to sulphone treatment.

Lepra reaction.—If this reaction occurs during the course of treatment the injections must be stopped, but if there is some complicating disease (such as malaria) this must be specifically treated. During the lepra reaction the patient should be confined to bed and the bowels freely evacuated. Alkalies are advisable: 60 gr. of sodium bicarbonate may be given four times daily. Intravenous injection of potassium antimony

tartrate, $\frac{1}{3}$ to $\frac{1}{2}$ gr. three times weekly, has proved an effective desensitizer. Calcium lactate and calcium gluconate in large doses act as adjuvants.

Treatment of pain.—Pain is usually associated with the lepra reaction, and there is increase of it and tenderness in the distribution of affected nerves. For this, adrenalin hydrochloride 1 in 1000 solution (0·2-8 ml. in 5 ml. saline) is infiltrated into the perineural tissues, or alternately, 0·02 grm. of ephedrine sulphate (dissolved in 10 ml. of a 0·5 per cent. sodium bicarbonate solution) given by the mouth, or injected similarly round the nerve, usually gives relief. Snake venom in small doses has also been found useful. In leprous neuritis, with cedema of hands and feet, aneurin (vitamin B₁), in 10 mgm. doses daily, is said to be successful.

Surgical treatment.—Excision of lesions.—If there is only one small skin lesion, say less than 1 inch in diameter, it should be excised. Large outstanding nodules should be shaved off, the base being touched with strong carbolic or nitric acid. The electric cautery or carbon dioxide snow have been similarly employed. The treatment of perforating ulcers is a difficult problem. Necrosed bone should be removed. Chronic ulcers with indurated margins may be stimulated by infiltration with hydnocarpus esters, and by applying sulphonamide powders or paste. Amputation is seldom necessary.

When the thickened ulnar nerve is constricted by dense fibrous tissue behind the condyle, or the peroneal nerve is bound to the head of the fibula, the thickened band may be severed. The nerve sheath may be slit

with benefit.

The eye.—As already indicated, sulphone treatment has special effect on eye lesions. Loss of vision is caused by changes in the cornea and plastic iridocyclitis.

The eye should be protected from trauma by wearing of tinted glasses. Pannus is best treated by peritomy which helps to prevent the spread of corneal opacification. Lepromata at the limbus are amenable to local therapy by application of solid carbon dioxide and diathermy, or by irradiation by Grenz rays in doses from 700 to 1,200 r.: the total amount varying from 5,500 to 11,600 r. For corneal ulceration in lagophthalmos a tarsorrhaphy should not be delayed. Cortisone drops should prove of value in clearing up corneal opacities and pannus. When the iris becomes involved the pupil must be dilated with 1 per cent. atropine drops. If the pupil fails to dilate, or if secondary glaucoma occurs, a broad iridectomy should be 'done. For muco-purulent conjunctivitis and palpebritis penicillin drops 2,500 units per ml. and penicillin ointment (1,000 units per grm.) are indicated. For chronic dacrocystitis the lacrymal sac should be removed (Kirwan, 1948).

The nose.—Special treatment is often required for the nasal ulceration. The crusts should be removed and the mucous membrane anæsthetized with cocaine and adrenalin or some caustic, such as trichloracetic or chromic acids (1 in 10 solution), applied and fulgurated with a diathermy apparatus. Sometimes douching with 2 per cent. sodium bicarbonate solution and painting with iodized hydnocarpus esters is also useful. For offensive discharge the following nasal lotion is used:

Sig.: $\frac{1}{2}$ oz. to be used with $\frac{1}{2}$ pint of water as a nasal douche.

Deformation of hands and feet.—Rehabilitation measures, such as carefully planned exercises, can often lessen deformities. The necessary movements may be produced in agriculture or textile industries, as carried out in the model Culion Island Colony in the Philippines. Modern plastic surgical methods have greatly improved the outlook, and the important contribution for the restoration of functions of the hand by P. W. Brand, of the Christian Medical College, Vellore, S. India, must be consulted.

Ulceration and loss of fingers are due to trauma and are to a great extent preventable. That serious attempts have not been made, until recently, to reconstruct the hands in leprosy is due to popular misconception: one is that paralysis is haphazardly progressive and therefore that healthy muscles used for transplantation may themselves become paralysed. The other is that leprosy lesions progress till fingers fall off, or become absorbed. Neither is true. The damage is due to ulceration, osteomyelitis, sepsis and gangrene. The leprosy paralysis is predictable in so far as it affects certain nerves, and then at certain anatomical levels. One can say that certain muscles may never become paralysed, however far the infection progresses. Those commonly paralysed are the intrinsic muscles of the hand, lumbricales, interossei, thenar and hypothenar eminences, flexor carpi ulnaris, flexor profundus to little and ring fingers. Sometimes paralysed are the extensors of the wrist, long extensors of fingers, thumb and abductor pollicis longus.

The chief disability is loss of grasp, due to inability to extend the interphalangeal joints, and loss of pinch, owing to the loss of abduction and opposition of the thumb. The surgical treatment follows the lines laid down by pioneers of hand surgery, such as Sterling Bunnell. After healing superficial sores, the hand must be mobilized as much as possible by physiotherapy. Next, operations must be performed for restoration of lumbrical action, using transplanted long flexors or extensors, then operation for restoration of opposition to the thumb. Finally there is a programme of rehabilitation. Brachial plexus block anæsthesia is used. For clawed fingers Bunnell's sublimis transplantation is the operation of choice, and interphalangeal arthrodesis for fingers with stiff joints. Details of anatomy and operative technique are described in Bunnell's "Surgery of the Hand." It is advised that only one side of each finger should be operated and the tendon transplants should be attached only to the radial side of each finger.

Trophic ulcers.—Cochrane advocates filling the cavities with 5 per cent. sulphonamide paste, bandaging or strapping and leaving for one week. The following is recommended:

Operative procedures are sometimes necessary. Metatarsalectomy is advocated. The limb should be devasculated by a tourniquet, and the bone disarticulated before removal. Local anæsthesia, adequately given, suffices, and the tourniquet should not be removed until the wound has been well packed with sulphonamide paste and a tight bandage applied.

Subsidiary measures.—The production of protein shock by intravenous injections of milk or other forms of protein sometimes causes temporary improvement and aids in healing up intractable ulcers, but must be used with caution. Rapid and favourable action has been claimed by some observers as a result. X-rays and radium have also been tried, and various baths, such as iron, copper sulphate and iron—arsenical baths at a temperature of 110° F. (in Java). Lowe has tried out cortisone and A.C.T.H. in the acute and subacute complications. Immediate response is excellent but fleeting.

Prophylaxis.—If children could be prevented from coming into contact with infectious cases, then the number of adults who would later become victims would be so few that the leprosy would decline. In planning preventive measures the incidence of child infection and of infectious lepromatous cases should be ascertained. If the former should reach 25 per cent. of the total and 20 per cent. of the latter, then intensive preventive measures must be undertaken.

The patients must be segregated in special areas near villages connected with a properly equipped centre. Infective cases in towns can be isolated solely in institutions. General hospitals should be prepared to treat leprosy in out-patient centres set apart for this purpose. Special research units should be developed, and special measures instituted for the care, segregation and observation of children with leprosy. Propaganda and carefully planned special training are essential.

A model leper colony is situated on Culion Island in the Philippines. It is a town with laundries, theatre and schools where some 8,000 lepers were originally segregated; at the end of ten years the numbers had been reduced to 3,000 by natural causes and almost complete cessation of new infections.

Since improvements have been made in the dietary, and intensive treatment has been given, especially good results have been obtained in children.

In no country should lepers be permitted to beg in the streets, keep shops, or handle food.

The prophylactic value of sulphones in the future management of leprosy has already been commented upon. The effect of B.C.G. injections as a means of prophylactic protection is now being investigated (Lowe).

 $^{^1}$ For a full account of modern leprosaria and their management, the " Practical Textbook of Leprosy" by R. G. Cochrane (1947), should be consulted.

CHAPTER XXXV

YAWS (FRAMBŒSIA)

Synonyms.—Pian; Frambœsia; Boubas (Brazil); Coko (Fiji); Parangi¹ (Ceylon); Dube (Gold Coast); Purru (Malaya).

Definition.—Yaws is a contagious inoculable disease, characterized by primary sore and indefinite incubation period, followed usually by fever, rheumatic-like pains, and the appearance of papules which generally develop into a fungating, encrusted, granulomatous eruption. Running a chronic course, it usually protects against a second attack. The disease is caused by Spirochæta pertenuis, and is controlled by salvarsan and bismuth salts. The organisms of yaws and syphilis are indistinguishable and the lesions produced are difficult to differentiate.

History.—The first descriptions, by Oviedo, of what we know as yaws did not appear until the sixteenth century. Before this period allusions in the literature appear to be mere surmises. Deductions from historical records suggest that yaws is of more ancient lineage than syphilis. It is clear that what we now know as syphilis appeared with dramatic suddenness at the end of the fifteenth century and, as a new and devastating disease, spread rapidly over Europe. According to records, the disease broke out after the return of Columbus to Spain. Oviedo (1478-1557) was in Barcelona at the time, and in his Historia General y Natural de las Indias, he stated that it was contracted from Indian women by the Spaniards who accompanied Columbus; that it was brought by them to Spain, and transmitted to the army of Charles VIII. Las Casas (1474-1556), in his Historia de las Indias, refers to a disease which was very dangerous to Spaniards, and was called syphilis, being known in Italy as the "French malady." Ruy de Isla, a physician practising in Barcelona in 1493, gives a very complete account and states that it was unknown before that year, and that it was brought by the crew of Columbus on their return from the first voyage to Haiti. Ruy himself treated several sailors from the squadron, including the pilot, Pincon of Palos.

In the autumn of 1493, Charles VIII of France invaded Italy with a rabble army. He captured Naples on February 22, 1495, but a new plague (syphilis), accompanied by severe skin lesions, broke out and necessitated the evacuation of the city. The spread of syphilis can be traced, according to Pusey (1933), with the dispersal of Charles's army throughout Europe. In 1497 it reached England and Scotland. In Japan it was not recognized till 1509 at Nagasaki, where it was attributed to the presence of Chinese and Portuguese sailors.

Syphilis, when introduced into a non-immune population, as in Uganda, in the nineteenth century, reproduced symptoms and manifestations recorded by our ancestors in the fifteenth; under these circumstances there is little doubt that syphilis can act as a devastating epidemic. According to the far-reaching researches of such authorities as Virchow (1896) and Elliot Smith (1930), no syphilitic bone of pre-Columbian origin has been discovered. On the other hand, Means (1925) and Williams (1932) have found the long bones of Indians showing evidences of syphilis in primitive races in North and South America; and the former found evidences of it in skeletons of the prehistoric mound-building Indians of Ohio.

¹ This word means "foreigner," a term applied by the natives to the European invaders of Ceylon.

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It is known that yaws often occurred in epidemic form on board slave ships and it may well be that the disease was an African importation into the New World. Much has been written of the possible identity in former times of such diseases as the "button scurvy" of Ireland, "sibbens" of Scotland and "rade. svge" of Norway and Sweden. It may well be that during the seventeenth and

eighteenth centuries they represented a severe form of syphilis.

Recent views on the syphilis-yaws question.—In Jamaica, Turner, Saunders. and Johnson record that no cardiac disease has been encountered in yaws cases. and this has been confirmed by radiographic examinations. In their critical survey of yaws in that island, they brought forward several new points. The "attack rate" in adults is as great as in children, and yet nothing like congenital syphilis has been seen in Jamaican babies, and this is held as strong evidence against the identity of syphilis and yaws. Infants and children in Jamaica are more liable to infection than are adults, and 90 per cent. of cases contract the

disease before they are fifteen years of age.

It may well be that yaws and syphilis have sprung from a common ancestor. In yaws it is probable that the spirochæte, under the more primitive conditions of the tropics, has spread from man to man by intimate contact, whilst the syphilitic spirochæte under more civilized conditions, where such contact is not possible, came to be communicated by the venereal route, thereby assuming a more virulent character and evolving (as do certain other spirochætes) neurotropic strains. Intermediate forms between the two classical forms of these diseases, which are so closely related as to be zoologically referable as "subspecies," undoubtedly have become evolved in time, as in the non-venereal childhood syphilis of the Arab tribes of the Euphrates and Iraq, known as "Bejel" (Hudson). This disease has been well described in Deir-ez-Zor in Syria, where there is a high incidence of syphilis, but very little gonorrhoea. This syphilis is spread by personal contact, is of low virulence, gives a positive Wassermann reaction, and corresponds to the endemic syphilis of Asia Minor described by von Düring. The most frequent lesions are in the mucous membranes of the mouth; but in other respects—in the special affinity for children. and in the production of hyperkeratosis and depigmentation—it resembles yaws. and circinate lesions of the soles of the feet, resembling crab-yaws, are common. Depigmentation of the dorsum of the hands resembles that described by Lacapère in Morocco, but Hoff and Shaby state that meningo-vascular lesions may still be observed amongst these peoples.

It is fair that some consideration should be paid to the expressed views of Hudson (1946). In its extended sense he thinks that "treponematosis" is a widely distributed disease caused by one species, T. pallidum, that this disease presents different clinical patterns under different climatic and sociological conditions; that any variations in the parasite itself are functional representing strains which may, or may not, have fixed biological characters. On this basis he includes yaws, syphilis, bejel and pinta under one heading and would thereby discount the theory of the American origin of syphilis as objectionable and as

just an historical fairy tale.

Geographical distribution.—Yaws is common in tropical Africa, West Indies, Ceylon, Pacific islands, Papua, the East Indies, and the Malay States. In India and China it appears to be rare. Children in the West Indies and Fiji are especially liable. During recent years it has become extremely prevalent in Kenya Colony, Tanganyika Territory, and Uganda, where it is spreading with great rapidity. On the other hand yaws has disappeared to a great extent from Guiana, Ceylon and Barbados, where it was previously extremely rife.

Epidemiology and endemiology. Contagion and heredity.—As yaws is highly contagious, all circumstances favouring contact with the subjects of the disease favour it. Simple skin-contact does not suffice; a breach of surface is necessary. The knowledge that the secretions from yaws lesions could transfer the disease to another person was well known to the slaves of the West Indies, and they practised auto-inoculation in their children who did not show a generalized eruption.

The disease frequently commences in a pre-existing ulcer, the organism (spirochæte) being conveyed by flies to the previously lacerated surface (p. 602). Cases originate in certain dirty houses, the virus from previous yaws patients seemingly impregnating the floors and walls of the filthy huts. In this manner the disease may be, and in some cases no doubt is, acquired without direct transference from an existing case. In some countries, as in Ceylon, yaws is a disease of the flat, low-lying districts, while practically absent from the hill country; in Assam, on the other hand, it is more common among the hill tribes than among dwellers of the plain. Ramsay has shown in Assam that native hill people, who only exhibit obscure lesions, such as condylomata, while living at high altitudes, develop florid yaws when they come down to the plains. In Jamaica, Saunders and Kumm have emphasized the importance of rainfall and geological formations on the distribution of yaws. Wherever there is porous limestone there is little or no yaws.

Yaws is neither hereditary nor congenital. A pregnant mother suffering from yaws does not give birth to a child suffering from the disease, nor one which will subsequently develop yaws, unless the virus be first introduced directly through a breach of surface after birth. It is not conveyed by the milk; nor does a suckling suffering from yaws necessarily infect its nurse.

This statement should be qualified by the well-known fact that a syphilis-infected mother does not inevitably transmit the disease to her offspring, and if she does transmit, she may do so irregularly, not to one child, but to the next, and to one only of twins.

Although two-thirds of the cases in the West Indies, Pacific Islands and Ceylon occur before puberty, no age is exempt. In Jamaica the peak of the infection rate is about eight years. No new infections are found after thirty. Three males appear to be infected to every one female. It has been frequently remarked that yaws shows a predilection for certain native races. On the whole, the negro and negrito stock is specially liable to severe attack.

Yaws at the present day shows a striking limitation to the tropics, but it is a disease so readily communicable by direct contact that it seems remarkable that it does not spread in temperate regions. In the tropics yaws is limited to low level areas, and to rural districts with primitive sanitation. In Haiti, for instance, yaws is the disease of distant villages, and syphilis with chancre is common in the main town. In the Philippines the same is true: in the country, yaws; in Manila, syphilis.

Ætiology.—In 1905 Castellani demonstrated in scrapings of yaws tissues an extremely delicate spirochæte—Spirochæta pertenuis, or Treponema pertenue—very like that of syphilis. To demonstrate this spirochæte, slides should be prepared from scrapings of an incised yaw papule before it has ruptured. The films may then be stained with Giemsa, or made by the indian-ink method; better still, the living parasites may be detected in fresh undried films by darkground illumination. A fully developed yaw is unsuitable, because it has been exposed to external sources of contamination and a variety of organisms will be present and may confuse the observer. Dobell and others have been unable to

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distinguish any structural differences between this spirochæte and S. pallida of syphilis (Fig. 234, 5, p. 918). With the aid of the electron microscope the appearance of flagella and an undulating membrane can be made out.

S. pertenuis has been found in the spleen, lymphatic glands, and bonemarrow; doubtless it also occurs in the blood. It is inoculable into monkeys and rabbits; in the former, especially in the orang-outang, it gives rise to lesions similar to those in the human subject.

Cultivation of S. pertenuis was successfully performed by Noguchi in ascitic fluid containing a piece of fresh animal tissue, such as the kidney, the whole being covered with a layer of sterile paraffin. This rather complicated technique has been simplified by the later work of Hata, who substituted horse-serum, the inoculation being made through the upper solidified layer. Strict anærobiosis is necessary.

Kumm has brought forward strong evidence that in Jamaica, at any rate,



Fig. 91.—Hippelates flies on a yaws ulcer. Showing method of spread by these insects. (Dr. L. A. León, Quito.)

a minute fly, *Hippelates papillipes*, carries the spirochæte from one person to another (Fig. 91). He collected the flies at the rate of 5,000 per hour from one ulcer; they crawl under the scab and ingest large numbers of *S. pertenuis*, which are afterwards regurgitated. *H. papillipes* is an oscinid fly having peculiar mouthparts, with projecting spines on the pseudotracheæ and labellæ (see p. 1062).

Inoculation into monkeys.—The most extensive and minute observations of Schöbl on Cynomolgus philippinensis with emulsified extracts of yaws lesions containing S. pertenuis deserve mention. The injections were made on the nose, eyebrows and scrotum. From three to five weeks after inoculation, papules appeared, corresponding to the typical yaw. Later, they spread peripherally like the ring-worm form of this disease. The disease in the monkey on first inoculation runs its course without developing into diffuse secondaries, but generalized yaws is produced by superinfection. Other late manifestations, such

as lupus-like ulcerations and keratoderma of plantar surfaces, resemble those seen in man.

Human inoculation.—The fact that the disease could be transferred by secretion from yaws lesions was well known to the slaves in the West Indies. Charlouis and others have inoculated yaws patients with syphilitic virus and have produced a chancre at a site of inoculation. Schöbl considers that S. pallida is panblastotropic with a tendency to invade and multiply in all tissues and produce lesions, but is mesoblastotropic in its tendencies. Syphilitic lesions are found in the skin, mucous membranes, bones and muscles, viscera and nervous system. The spirochætes invade the cardio-vascular system and enter the placenta, giving rise to congenital syphilis. The yaws spirochæte is epiblastotropic,



Fig. 92.—Primary yaws chancre on foot. (Dr. L. A. León, Quito.)

invading certain tissues, particularly the skin and bones; the nervous and cardiovascular systems are not usually invaded and the disease is not congenital. It is suggested that in the few instances, in which lesions of the internal organs and cardio-vascular system have been reported, co-existing syphilis has not been rigidly excluded.

Yaws, moreover, shows a striking limitation to the tropics, and the effect of climate upon it is such that it does not spread in temperate climates from cases which are introduced. It is more common at low altitudes and in areas with higher rainfall.

Yaws spirochætes are unable to penetrate unbroken skin surfaces. Autoinoculation may occur during the early course of the disease in man; the infection may spread to other parts of the skin, but mucous membranes are not invaded.

Other animal inoculations.—Nichols originally showed that yaws, like syphilitic lesions, can be produced in the testis of the rabbit, though the incubation period is shorter. Pearce and Brown observed, in intratesticular inoculation with

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S. pertenuis in the rabbit, a granular and finely nodular periorchitis, a lesion different from that of S. pallida. Turner and Chesney in Haiti found that in rabbits injected with S. pertenuis the testicular lesions consisted of miliary granules in the tunica and epididymis, but that general enlargement and induration (so common after inoculation with S. pallida) do not occur.

Pathology.—A feature of yaws lesions is the great thickening of the epidermis and degeneration in the epithelial cells. In later stages there may be hyperkeratosis. The elongated papillæ are vascular, and are infiltrated with lymphocytes; leucocytes and plasma cells are also numerous. In contrast with syphilis, perivascular infiltration in the corium is absent, and there is no endarteritis as in syphilis. Dupont and Dubois describe the primary lesion as an epidermic papule of which the centre becomes necrotic and leads to ulceration. Cellular infiltration is limited. In contradistinction, the syphilitic chance erodes the



Fig. 93.—Primary yaws sore on lips of Australian aborigine child. (Dr. H. Basedow, Adelaide.)

epidermis and extends more deeply. In secondary yaws large papules are formed by inflammatory infiltration with hypertrophy of the epidermal ridges. In the gummatous stage the essential feature is dominance of the epithelioid elements in the infiltration.

Symptoms.—As in syphilis, the symptoms of yaws can be divided into three stages—primary, secondary, and tertiary.

Primary Lesion (madra buba or "mother yaw") (Fig. 92).—According to Sellards the incubation period in experimentally-inoculated yaws in man is three and a half to four weeks; in experimental apes it may be as long as three months. Naturally-acquired yaws is reputed to have, as a rule, a longer incubation period than the inoculated disease. The primary lesion may appear as a granuloma, or a papule, at the site

of inoculation, 1-7 cm. in diameter, and is known as the "frambœsoma." It may develop at the site of some old skin lesion. It is ordinarily extragenital, but may be situated on any part of the body: the buttock, thigh, knee, leg, arm, breast, or lip (Fig. 93), but is rare on the scalp. The lower part of the leg is the site of predilection; the breasts of nursing women and the mouths of suckling babies are not uncommon sites. In Moss and Bigelow's large series the genitalia were the seat of the primary lesion in only 1 per cent. In native women it is frequently observed at the bend of the elbow, or on the hip, and is contracted in this situation from carrying children who are infected with the disease. The primary lesion may be so small as to escape detection; it may be single or multiple, and, in fact, great difficulty may be experienced in differentiating it from allied cutaneous lesions, but, as a rule, it is remarkably persistent, lasting from two to four months, and it may persist for a year or more.

According to the Jamaican Yaws Commission, the primary lesion is found on the lower extremities in over 70 per cent. of cases. In 39 cases it was found:—

On head, face and neck in 1
On upper extremities ,, 4
On genitalia ,, 1
On leg ,, 12
On ankle and foot ... 21

The lesion, on becoming larger, becomes covered with a yellowish secretion or scab. It is at this stage known as the "mother or master yaw," the "mama pian" of the French. In ordinary locations yaws lesions are not painful, unless firmly pressed.

The appearance of the lesion is preceded by a certain amount of constitutional disturbance. The intensity of the general symptoms varies within wide limits; sometimes they are hardly perceptible, so are not complained of, but usually there is well-marked malaise with rheumatic pains. Occasionally there is severe constitutional disturbance lasting for about a week, with rigor, smart fever (100° to 103° F.), persistent headache, pains—worse at night—in the long bones, joints and loins, and sometimes gastric disturbance and diarrhœa, especially in children. The lymphatic glands in the immediate vicinity become enlarged. During the decline of these constitutional symptoms the secondary eruption appears. The Wassermann reaction becomes positive three to four weeks after the primary lesion and rapidly grows stronger in titre.

SECONDARY STAGE.—This is ushered in by a fine, light-coloured furfuraceous desquamation. The skin becomes harsh and dry, loses its natural gloss, and here and there patches of desquamation (best appreciated with the aid of a hand lens) are formed. These patches are mostly small and circular; occasionally they are oval, irregular, or form rings encircling islets of healthy skin scattered irregularly over limbs and trunk; sometimes they are almost confluent, the patches coalescing and making the skin look as if it had been dusted over with flour. On the other hand, this furfuraceous desquamation may be so slight as to be overlooked. In some instances the heaping-up of desquamating epidermic scales produces white depigmented patches, very evident on the dark skin of a negro or oriental.

This patchy, furfuraceous condition of the skin may persist throughout the attack, or may reappear as a fresh eruption at any time in the course of the disease. It has been described by Schöbl and Sellards as "keratoid exanthem" in artificially-inoculated yaws.

Appearance of the yaw (Fig. 94).—When the furfuraceous patches have been in existence for a few days, minute papules appear in them. This very characteristic eruption, from which the disease takes one of its names—frambæsia (or raspberry)—breaks out three months after the primary lesion. These secondary lesions may vary in size from a pin's head to half a crown and, according to Spittel, begin around the primary sore ("mother and daughter yaw"). The itching is usually considerable. As in syphilis, the eruption may be very pleomorphic; it may be roseolar,

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or consist of macules with desquamation resembling a squamous syphilide. It may appear on any part of the body, especially in exposed situations and on the anterior surface. The papules occur in groups, the larger appearing to be surrounded by a group of satellites, which has given



Fig. 94.—Secondary yaws in a Malay boy. (W. E. Le Gros Clark.)

rise to the various native designations for yaws. Auto-inoculation is probably responsible for the appearance of these lesions in symmetrical fashion, whenever the skin or mucous surfaces come into intimate contact; they are present at the angles of the mouth, in the axillæ, in the anal cleft, and in the inguinal region; in contradistinction to syphilis, they are rarely present on the true mucous surfaces, but often in clusters just

inside the nostril. Several of the groups may coalesce to cover a large surface.

The yaw is pushed up from the rete Malpighii through the horny epidermis, which breaks over the summit and splits in radiating lines from the centre, the necrosed segments curling away from the increasing papule. Soon a yellow point appears around a hair follicle, consisting of a cheesy-looking substance which cannot be wiped away, unless undue force is used.

From this stage the papule may either cease to grow, the apex becoming depressed, or may go on to form the typical yaw. In the latter case the lesion gradually grows into a rounded excrescence, the yellow material at the top widening out so as to form a complete cap encrusting the little tumour. The smaller tumours are hemispherical; the larger are more flattened, or even depressed at the centre, possessing everted, somewhat overhanging, rounded edges. Occasionally, though rarely, a big yaw may include an area of sound skin.

The firmly adherent crust which caps and encloses an uninjured yaw is yellowish, granular, blotched with blood-stains and encrusted dirt. Deprived of its crust, the little swelling is seen to be red, generally smooth and rounded on the surface, and oozing pale yellowish serum in which spirochætes may be demonstrated; when inspissated, this serum forms a fresh cap to the yaw, and on microscopic examination is found to be teeming with the organisms. According to size, it stands out anything from $\frac{1}{8}$ to $\frac{3}{4}$ in. above the surrounding healthy skin. Pus, unless a consequence of irritation, is not, as a rule, found under the crust.

Although the formation of the papules and yaws is attended with much itching, the yaw itself is not at all sensitive; the tumour may be touched, with acid even, without causing pain—a diagnostic point of some importance. Sometimes, as in syphilis, the eruption has a circinate character, the so-called "ringworm yaws." The itching of yaws lesions is a point of differentiation from syphilis, but, as Blacklock has pointed out, native races are also exposed to insect bites and dirt.

The yaw usually attains its maximum development in two weeks. For several weeks longer it remains stationary before beginning to shrink. The crust then thins, shrinks, darkens, separates at the periphery, and at last falls off, disclosing, at the site of the former fungating mass, a slightly thickened spot of fairly sound skin, which, though pale at first, may sub-

sequently become hyperpigmented.

Sometimes the secondary rash takes on a papular appearance, when the lesions are known as "acuminate papules." These are symmetrically distributed over the back, shoulders, arms, elbows and knees, and much resemble a follicular syphilide. Secondary lesions may last from six months to a year. Simultaneously with the eruption, as in secondary syphilis, there may be a uniform, painless enlargement of the lymphatic glands, in the aspirated lymph of which the specific spirochæte may be demonstrated. When the lesions subside, pigmented spots remain, as in secondary syphilis, and are specially noticeable on the palms of the hands.

Lichenoid eruptions.—Lichen frambæsianus ("Pian datre") is a lichenoid generalized eruption of the skin described by Dutch writers in

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Indonesia. It is a micropapular eruption which is very striking in appearance and is not associated with yaws papules. It is, of course, analogous to secondary lichenoid eruptions in syphilis, and must be distinguished from other lichenoid eruptions, such as lichen ruber planus, lichen pilaris and lichen scrofulosorum. It is now generally recognized as an early secondary manifestation in children and young adults, the same condition as has been described by Nicholls as "furfuraceous desquamation" and by German writers as the early "frambæsiform efflorescence." The lichenoid eruption is apt to occur in patches over the shoulders and, according to Deibel and Elsbach, there is a tendency to hyperpigmentation of the peripheral micropapules, associated with depigmentation of the centre.

The serum of patients in the secondary stage gives marked positive Wassermann and Kahn reactions, and this makes the differential diagnosis from syphilis impossible by these means.

Tertiary stage.—It sometimes happens that the tumours, instead of becoming absorbed, break down and ulcerate, the ulceration, which may last for years, being confined to the yaw itself. In other instances



Fig. 95.—Tertiary yaws ulceration on forearm of European.

ulceration goes deeper and extends circumferentially, giving rise to extensive sores with subsequent cicatricial contractions. Such ulcerations occur in about 8 per cent. of cases and may or may not be encrusted. (Fig. 95.) With the development of the deeper and wider forms of ulceration, the typical lesions of yaws may disappear for a time, or perhaps permanently. In the latter case the ulcers are said to be non-infective. Ulceration of the greater part of the limbs, especially the leg and ankle, may take place. Tertiary manifestations are seldom observed in cases which present late secondary lesions. The serum of these cases gives positive Wassermann and Kahn reactions, but the cerebro-spinal fluid,

in cases of advanced ulceration of the nose and other parts of the body, gives a negative reaction with a normal cellular and biochemical picture.

Lesions of the hands.—A scaly condition of the palms of the hands may persist for years. Multiple dactylitis, with uniform swelling of the phalanges, onychia, paronychia, atrophy of the nails, and subsequent deformity, is often observed. (Fig. 96.)



Fig. 96.—Tertiary yaws. Onychia of fingers. (W. E. Le Gros Clark.)

Foot yaws ("Dumas," or pink parangi—Ceylon; "crabs," or "crab yaws"—West Indies).—When a yaw develops on the sole of the foot it causes much suffering because it is bound down by the dense and thick epidermis. Spreading laterally under the thick, leathery and unyielding epidermis, it may become large. After a time the epidermis over the growth gives way, splitting up in a radiating fashion (Fig. 97). Pressure being thus removed, the yaw fungates, and suffering

in cases of advanced ulceration of the nose and other parts of the body, gives a negative reaction with a normal cellular and biochemical picture.

Lesions of the hands.—A scaly condition of the palms of the hands may persist for years. Multiple dactylitis, with uniform swelling of the phalanges, onychia, paronychia, atrophy of the nails, and subsequent deformity, is often observed. (Fig. 96.)



Fig. 96.—Tertiary yaws. Onychia of fingers. (W. E. Le Gros Clark.)

Foot yaws ("Dumas," or pink parangi—Ceylon; "crabs," or "crab yaws"—West Indies).—When a yaw develops on the sole of the foot it causes much suffering because it is bound down by the dense and thick epidermis. Spreading laterally under the thick, leathery and unyielding epidermis, it may become large. After a time the epidermis over the growth gives way, splitting up in a radiating fashion (Fig. 97). Pressure being thus removed, the yaw fungates, and suffering

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diminishes. Crab yaws may last a lifetime after infection in childhood. Chesterman suggests that in the foot lesions a fixation point for S. pertenuis is formed. A condition known as "clavus" in Dominica results from the healing of these granulomata; the centre of the core drops out, leaving an irregular erosion of the sole of the foot, or there may be deep fissures or cracks. Similar pitting occurs on the palms of the hands. According to Sayers, this is the commonest lesion of yaws in the Solomon Islands, and causes great disability, especially in children; when bilateral it incapacitates them from walking.

Gangosa (derived from the Spanish meaning "muffled voice"), or destructive ulcerous rhino-pharyngitis (Fig. 98), which is now generally



Fig. 97.—Foot yaws, or "crab yaws." (Dr. J. D. Reed.)

regarded as a sequel of yaws, usually commences as an ulcer on the soft palate. Slowly spreading, it may make a clean sweep of the hard palate, the soft parts, cartilages and bones of the nose, sparing the upper lip, which is left as a bridge across a great chasm, the floor of which is formed by the intact tongue. A most offensive odour is given off from the ulcerated surface. The disease may he arrested spontaneously at any period of its progress, and long before such extensive mutilation as that described has been effected: but it is always a longstanding and chronic affair and may linger as an indolent ulceration for years. As a rule, the larynx is spared; but. although phonation may be retained, articulation is seriously impaired. Gangosa occurs at any age, but is rare in young adults, though Leyes states that in Guam he

has seen it in children of 3, 4, and 9 years of age. It is very common in parts of the West Indies (Dominica, 60 cases in a population of 2,000), Guam (1.5 per cent. of the population), the Carolines, Fiji, Ceylon, British Guiana, and West, Central, and East Africa. It is often found associated with the bone lesions of yaws.

Goundou, or Anákhré ("Gros Nez"). —In 1882 MacAlister drew attention to what were termed the horned men of Africa, and in 1887 Lamprey gave further details illustrated with drawings. The natives call the disease goundou and anákhré. Later observations show that it has a wide distribution in Central Africa and South America, and that a similar disease occurs in the larger apes, chimpanzees, and baboons. An ancient Inca skull from Peru, described by Letulle, shows the characteristic lesions of goundou.

Stannus and Hamerton have shown that in the apes the hyperostosis is probably the after-result of osteitis cystica.

Goundou usually commences during childhood, although adults may be attacked. The earliest symptoms are severe and more or less persistent headache which, after a time, is associated with a sanguino-purulent discharge from the nostrils, and formation of symmetrical swellings the size of a small bean at the side of the nose. Apparently the swelling affects the nasal process of the superior maxilla. The cartilages are not involved. After continuing for six or eight months, the headache and discharge subside. The paranasal swellings persist, and continue slowly and steadily to increase until in time they may attain the size of an orange, or even of an ostrich's egg. As they grow, the tumours, encroaching on the orbits, may interfere with the line of

vision and finally destroy the eyes. In severe cases there is a general diffuse hyperostosis of the anterior part of the maxilla. There is no pain in the tumours themselves. The superjacent skin is healthy and freely movable. The tumours are oval, with the long axes directed downwards and slightly from within outwards (Fig. 99). The nostrils are bulged inwards and more or less obstructed. The hard palate is often affected. resulting in the most hideous deformity. General glandular enlargement may be Trauma seems to predispose to the development of goundou.

A case of goundou associated with tertiary syphilis was described in London by Sharpe. The patient had never been in the tropics. The lesions resembled the paranasal swellings so characteristic of goundou.



Fig. 98.—Gangosa in an Australian aborigine. (Dr. H. Basedow, Adelaide.)

According to recent accounts, cases of goundou in Jamaicans invariably give a positive Wassermann reaction.

The bony outgrowths, not necessarily bilateral, are attached to the nasal bone and nasal process of the maxilla, but, according to Botreau-Roussel and Clapier, they are not entirely confined to this region; a similar hyperostosis may co-exist on the tibia, upper or lower jaw, forearm, femur, or clavicle. There is a general opinion at present that goundou is a systematized hypertrophic osteitis connected in some way with yaws.

The bony changes of goundou consist of hyperostosis, which may be limited to the ascending or nasal processes of the superior maxilla, or be more widespread and affect the other bones of the skull as well, with an ever-present tendency to the formation of bosses of overgrowth and to the obliteration of adjacent

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cavities. The underlying pathological process is an osteo-periosteal dyscrasia and the end-result is the production of finely-porous bone.

As yaws and syphilis are so closely allied, it might be expected that similar lesions might be found in the generalized osteitis of syphilis, but there appears to be very little evidence of it. There is very little difference between the bony changes of goundou and those which have been called *leontiasis ossea*, and, according to Stannus, hyperostosis of the facial bones has also been recorded in Paget's disease—osteitis deformans. According to modern knowledge, it seems possible that goundou is more akin to osteitis fibrosa, due to interference with the



Fig. 99.—Goundou. (Dr. P. M. Shepherd.)

bony metabolism and an endocrine disorder, and it may well be that in this instance yaws constitutes the non-specific factor acting on an ill-fed native child population. Goundou-like swellings in horses, monkeys and young pigs ("cachexie osseuse") point to osteitis fibrosa as the initial stage of this condition and all changes between cystic disease of the bones and hypertrophic exostosis can be traced in a series of skulls.

Treatment consists in incising and displacing the periosteum and chipping away the bony outgrowth with a chisel. Early cases, according to Botreau-Roussel, yield to intravenous and intramuscular injections of neosalvarsan, four or more injections being necessary before improvement is observed. This observer operated with success upon 113 out of 130 cases observed on the French Ivory Coast and the reader is referred to his monograph (Masson et Cie., 1925) for further information.

Periostitis, osteitis and epiphysitis (Figs. 100, 101, 102).—Circumscribed painful periosteal nodes are frequently found on the anterior aspect of the long bones, especially the radius, ulna, and tibia. The swellings are hot and exquisitely

tender, and the superjacent skin is tense and stretched. After the subsidence of the acute stage, hard, firm periosteal nodes remain. A diffuse osteitis may result in a sabre-shaped deformity of the long bones, especially the tibia and occasionally the arms and fingers. A rarefying process is also at work, for such bones are subject to spontaneous fracture with resulting malunion, accidents which are common in districts in which yaws is endemic. Hackett, who has studied the sabre-shaped tibiæ of the aborigines of Australia, believes that syphilis does not occur among these peoples, and that the bone lesions are due to yaws. Colloquially known as "boomerang leg," the deformity is an anteroposterior curvature below the knee with a forward convexity; occasionally there are bosses of localized periostitis. Radiographs show that areas of

rarefaction appear early, and the bone becomes deformed. The appearances depend upon the severity of the initial lesion and the time which has elapsed since the onset of the disease. Other lesions of yaws, including gangosa, have been noted in Central and Northern Australia. A chronic periostitis of the clavicle is frequent in Fiji. These bone changes are accompanied by intense rheumatic pains, and have received distinctive names, such as "sasala."

Juxta-articular nodules.—Fibrotic tumours situated over the olecranon, the lower end of the femur, and in other situations on the long bones, are regarded as a tertiary phenomenon of yaws, and Sobernheim has demonstrated spirochætes in them by the silver-impregnation method of Levaditi. Formerly they were regarded as constituting a disease sui generis, but those



Fig. 100.—Distortion of fingers in tertiary yaws.



Fig. 101.—Tibial periosteal nodes, ulcers, and deformity of phalanges in yaws.

cases which have been investigated invariably give a positive Wassermann reaction. Originating subcutaneously, these nodules may reach the size of a small orange (Fig. 103). Chambers in Jamaica found these nodules in endemic yaws in rural areas and in only nine children under fourteen years of age. Tiny nodules may be felt as early as one to two years after infection, but they usually appear after a lapse of 15–40 years. It is also pointed out that, when bones lesions are present, the nodules tend to form in their vicinity. They are remarkably painless, and very rarely ulcerate or suppurate. Juxta-articular nodules are generally multiple, usually in the neighbourhood of the joints, but, according to Steiner, may also occur scattered over the body. Similar lesions were first described by Jeanselme in 1899 in tertiary syphilis, and since that time the Spirochæta pallida has been isolated from them (Hu and Frazier), while Hudson found the same nodules in "bejel," the non-venereal syphilis of the Arabs, among whom they occur in 2·1 per cent. of the adult male population and are known locally as "rik."

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According to Frontoynant and Girard, they often contain uric-acid crystals. In Africa they are apt to be mistaken for Onchocerca volvulus cysts.

Skin lesions.—Healing of subcutaneous gummata is frequently followed by depigmentation of the skin, resulting in light-coloured or leucodermic patches, especially visible in native races. A macular depigmented exanthem limited to the hands, wrists, feet and ankles is pathognomonic of yaws and was first described by Ziemann as "melung."

The radiographic appearances of the bone lesions of yaws in Uganda



Fig. 102.—Tertiary bone lesions.

have been intensively studied by Hackett. Apart from the absence of osteo-chondritis in yaws, there is probably no bone lesion that occurs in one disease that may not be observed in the other.

Secondary cases show focal rarefaction in the cortex, periosteal deposits in which rarefactions also occur. Although in many lesions the bones finally return nearly to normal, sometimes cortical thickening and bone expansion result and may lead to increased convexity of its anterior profile (sabre tibia).

In secondary bone lesions, and to a less extent in tertiary lesions, spontaneous resolution takes place in a few months. Next to the tibia the ulna is most frequently involved; next in frequency are the hand, and lastly the footbones and radius. No changes are found in joints. Periosteal deposits indicate active periostitis: cortical rarefactions and rarefying osteititis. Periosteal deposits can be regarded as an osteoperiostitis.

After effects.—Contractions resulting from scar tissue may lead to partial ankylosis of joints, in severe cases to the destruction of lymph-channels and to the production of elephantiasis in the affected limb.

Synovitis.—Chronic synovitis, analogous to that of tertiary syphilis often associated with bone lesions, and, it may be, with disorganization of the joint, has been recorded.

Ganglion and other lesions.—The frequency of tenosynovitis and ganglion-formation in the region of the wrist was noted by Graham, Moore, and other observers (Fig. 102). These ganglia are usually associated with tenosynovitis and, as extra proof of their origin, they both respond in a remarkable manner to treatment with neosalvarsan and bismuth. Stricture of the mouth due to tertiary yaws has been recorded.

The general health.—Except during the initial fever, or during one of the recurring febrile relapses, the general health is not, as a rule,

affected. Occasionally, however, there are debility and cachexia; or there may be enlargement and tenderness of the lymphatic glands. In other instances rheumatic pains may be very severe.

Immunity.—After the subsidence of the secondary stage immunity

is produced, but Sellards and Goodpasture demonstrated that this is relative only, for they successfully reinoculated with the disease patients who had undergone a course of salvarsan treatment. Apparently, saturation of a community with yaws virus produces a relative immunity to syphilis. these grounds may be explained the well-authenticated fact that syphilis is absent amongst the Polynesians of Fiji. Tonga and Samoa, in whom yaws is especially prevalent. Formerly Fijians were in the habit of inoculating their children against yaws to protect them from subsequent attacks. As far as accurate experiments have gone, immunity in syphilis is acquired much earlier than in yaws. Now that yaws has been eliminated in Suva and surrounding districts, the third generation of Fijians reared in these surroundings is now becoming infected with syphilis, and the congenital form in children has been observed.

Duration and recurrences.—Yaws lasts for weeks or months or years, its duration depending on general health, idiosyncrasy, hygienic conditions, and



Fig. 103.—Juxta-articular nodules. (Photo: Dr. Watt.)

the treatment. Mild cases in healthy subjects terminate in about six weeks, though the average duration of an attack is estimated at about one year. In other instances, especially in the debilitated, the disease runs on for months, successive crops of eruption being evolved. Sometimes these recurrences may stop short at the stage of desquamation, or at the papular stage, or they may proceed to the formation of typical yaws. They are usually preceded by feverishness, pains in the bones and joints, and the successive crops may either be limited and partial in their distribution, or general.

Sequelæ.—Contrary to general opinion, Harper in Fiji believed that late manifestations of yaws occur as in syphilis and that they produced neurological conditions resembling those of locomotor ataxia and general paralysis. Lambert recorded in the South Pacific 42 Melanesians and Polynesians who died in Samoa of G.P.I.; furthermore that aneurysmal dilatation and aortic disease were comparatively common.

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Chossier, in routine post-mortems in Haiti, found aneurysms and other arterial degenerations in chronic yaws, but more recent writers (Blacklock), in assessing the clinical differentiation of yaws and syphilis, have once more remarked upon the comparative rarity of visceral and neurological lesions of the latter amongst native races. In yaws the Wassermann reaction of the cerebrospinal fluid has been generally found negative, especially in the tertiary stages. Chesterman emphasized the comparative frequency of new growths following yaws and has recorded melanoma, amplanted upon crab yaws of the foot.

Mortality.—Although in the literature reference is made to deaths from yaws, yet, judging from the statistics collected by Nicholls, the mortality must be small indeed.

Diagnosis.—A painless, insensitive, larger or smaller, circular, encrusted red, granulomatous excrescence occurring in an endemic district is almost certainly yaws. The most important point about yaws, both in diagnosis and in ætiology, is its relationship to syphilis. Both diseases may occur in the same individual (Powell cites two cases, and Charlouis two, of syphilis supervening on yaws); and antecedent syphilis certainly does not confer absolute immunity to yaws, nor antecedent yaws to syphilis. The serum in both diseases gives a positive Wassermann reaction. Yaws may die out in a community, as in British Guiana (Daniels), yet syphilis remain; yaws may be universal in a community, as in the Fijians, Tongans and Samoans, and yet true syphilis, whether as an acquired or as a congenital disease, be, until recently, unknown. In yaws, Hutchinson's famous syphilitic triad—the characteristic notched teeth, nerve deafness, and interstitial keratitis—are absent.

Table IX shows the main points of differentiation.

TABLE IX

Yaws

Not congenital. Primary sore—extragenital.

Secondary stage

- (a) Typical yaw pathognomonic; furfuraceous desquamation and plantar lesions characteristic.
- (b) Mucous membranes not affected.
- (c) Itching common.
- (d) Alopecia unknown.
- (e) Eyes unaffected.

Tertiary stage

- (a) Visceral lesions absent.
- (b) Nervous system not usually affected.

Syphilis

Congenital.

Primary sore—usually genital.

Secondary stage

- (a) Seldom imitates frambæsia.
- (b) Mucous membranes affected.
- (c) Itching rare.
- (d) Alopecia may occur.
- (e) Iritis common; choroiditis and retinitis rare.

Tertiary stage

- (a) Visceral lesions occur, e.g., pericellular cirrhosis, gumma of liver, kidney.
- (b) Nervous system liable to infection: tabes, G.P.I.

Table IX: continued

Tertiary stage

(c) C.S. fluid always negative Wassermann (Fischer; Turner, Saunders and Johnson).

(d) Blood-vessels: no endothelial proliferation as in syphilis.

Yaws better resisted. Constitutional disturbance slight; great exuberance of eruption and cheloid scarring.

Does not respond to mercury.

Tertiary stage

(c) C.S. fluid usually positive Wassermann.

(d) Endarteritis obliterans of viscera—cerebral thrombosis.

Syphilis attacks constitution, affecting the vital structures.

Responds well to mercury.

Secondary yaws may have to be differentiated from bromide rashes.

TREATMENT

General measures.—All are agreed on the propriety of endeavouring, by good food, tonics and occasional aperients, to improve the general health. Most are agreed on the propriety of endeavouring to procure a copious eruption by stimulating the functions of the skin—by warm demulcent drinks; by a daily warm bath with plenty of soap; and, during the outcoming of the eruption, by such diaphoretics as liquor ammoniæ acetatis and guaiacum. Warm clothing is indicated. In crab yaws a local application of 2 per cent. tartar-emetic ointment in vaseline is very useful.

I. Salvarsan, neosalvarsan (Neoarsphenamine¹).—Except where much bone destruction has taken place, salvarsan, or better still its more recent and more soluble derivatives, has a curative effect upon yaws in every stage of the disease. The most generally used drug at the present time is neosalvarsan (neoarsphenamine). It is given intravenously to adults, and, if possible, to children; or intramuscularly (0·4 grm. dissolved in oil, into the buttock). The more urgent symptoms yield much more rapidly than do those in syphilis, and relapses are not so common. Since the introduction of salvarsan the natives of the Congo dislike being treated until the secondary rash is well out. For adults the intravenous dose advocated is 0·6–0·9 grm.; for young adults 0·6 grm., for children up to ten years of age 0·3 grm., and for children under two years, 0·1 grm.

The systematic use of neosalvarsan in a yaws community would, if thoroughly carried out, promptly get rid of the endemic disease, and, wherever possible, it should be enforced. The average time to effect a clinical cure is eleven days. In Samoa it has been found necessary to give three injections of 0.6 grm. of neosalvarsan, at weekly intervals, for an adult male, and appropriately smaller doses for women and children. Babies are treated by intramuscular injections. Moss, in San Domingo, found that the cure after three injections is permanent. The great objection to mass treatment of native populations with the salvarsan compounds is their cost. Apparently, mercury and potassium iodide have little therapeutic action in yaws of adults as compared with syphilis, but in breast-fed children these drugs will cure the infant through the mother's milk.

 $^1\,\rm Throughout$ this account the terms are phenamine and neoarsphenamine are given as the American equivalents of salvars an, neosalvarsan, etc. 618 YAWS

II. Bismuth.—The successful treatment of syphilis by Fournier with sodium-potassium-bismuth tartrate led to the adoption of a similar method in yaws. The considered opinion of workers is that none of the many bismuth preparations can be said to take the place of the synthetic arsenicals in African yaws and syphilis. The most active form appears to be the sodium tetra-bismuth tartrate in both secondary and tertiary yaws.

All preparations act more efficaciously when given in the early stages. Injections should be made deep into the subcutaneous fascia, and occasionally some induration and abscess-formation may result. When treating natives on a large scale, a soluble form of sodium-bismuth tartrate $(Sobita^1)$, is preferable. The dose is 0·2 grm. (8 gr.) dissolved in 2 ml. of distilled water, 10 per cent. solution, or in oil injected intramuscularly; for children up to two years, $\frac{1}{2}$ -1 gr.; from two to eighteen years, 1-2 gr.; and for aged persons, $1\frac{1}{2}$ -2 gr. The generally accepted dosage for an adult is $1\frac{1}{2}$ -4 gr. twice weekly with a total dosage of 6-14 gr. Children tolerate relatively larger doses than adults. Since 1924, over a million cases have been treated in Tanganyika alone by this method.

In patients with septic mouths, stomatitis and albuminuria are apt to ensue as a result of this bismuth treatment. Other toxic effects are diarrhæa and skin rashes, while lassitude and articular pam occur in some cases. This, and the fact that three or more injections are necessary, have been the greatest objections to the general use of bismuth, especially in the Solomon Islands and the Congo. On the whole, the toxic effects of bismuth are less frequent and are milder than those of mercury and salvarsan. In Jamaica, the dioxide of bismuth is preferred, and next in favour is the oxychloride. Bismuth salicylate is also used in 10 per cent. suspension in olive oil. In Jamaica six to ten treatments are given.

- III. Combined treatment.—Combined neo-bismuth treatment is effective. By combining bismuth and neosalvarsan (neoarsphenamine), in alternating weekly injections, the chances of severe reactions are reduced. Neosalvarsan is given intravenously and bismuth intramuscularly.
- IV. Arsenical preparations given by the mouth.—Stovarsol is given in 1 grm. doses daily, increasing to $1\frac{1}{2}$, 2, and 3 grm. on successive days for adults; $\frac{1}{2}$ -1 grm. for children. After a total of 8–15 grm., according to van den Branden and Lefrou, the Wassermann reaction becomes negative. Chesterman considered three courses necessary to effect a cure, but found that he could give in stovarsol ten times the corresponding dose of neosalvarsan. One objection to stovarsol is that the full course may be more expensive than injections of salvarsan. Halarsol, in intravenous and intramuscular injections, in doses of 0·125–0·25 grm. for three doses at three- to four-day intervals, has been proved on the Congo to be efficacious in all stages of yaws. The minimal toxic dose is 4·5 mgm. per kilo.
- V. Penicillin.—As first established by Lourie and Collier (1943) penicillin has a remarkable specific action on the syphilis spirochæte and this knowledge has been used in the treatment of yaws, where, as far as

¹ This preparation is placed on the market by Howards & Sons Ltd.

can be at present ascertained, the results of penicillin are even more satisfactory and are readily appreciated by the native population. A number of papers have appeared in the last eight years, mostly by American workers in the Pacific war zone. The results are most striking in the primary and secondary stages. Thus Whitehill and Austrian (1944) described the treatment of 41 primary and secondary cases in Fijians, in whom spirochætes were demonstrated by dark-ground illumination. Thirty were under fifteen years of age. Penicillin was injected intramuscularly in doses of 15,000-30,000 units at intervals of 3-4 hours to a total dosage of 100.000-2,400,000 units. All lesions were completely healed in three weeks and spirochætes disappeared from the lesions after 16 hours. Lofgren (1944) reported a case in a European who received 11 mega units and by the twelfth day all lesions had healed. Findlay, Hill and Macpherson had a similar experience in West Africa and witnessed complete healing of a primary yaw in 6½ days. Further reports show a remarkable agreement, such as those of Tompsett, Kauer, and Guimaræs. South America confirmatory evidence is forthcoming, but with smaller doses. In seven patients all external evidence of vaws disappeared between the twelfth and forty-fourth days of treatment and serological reactions became negative on the sixtieth day (da Cunha, Leão and Guimaræs, 1945). Flock and de Lajudie now give 100,000 Oxford units of sodium penicillin in sterile olive oil by intramuscular injection in the secondary stage. The individual dosage is 1 ml. of oily suspension containing 10,000-15,000 units daily for seven days or longer.

Procaine penicillin is superior because it is slowly absorbed, and therefore injections can be made much less frequently. By this method adequate serum concentration can be maintained above 0.08 units per ml. for a period of 72–96 hours. Procaine penicillin is given in arachis oil, jelled with 2 per cent. aluminium monostearate in the following schedule: on the first day injection of 4 ml. procaine penicillin (1.2 mega units), then one daily for six additional days, or 2 ml. twice a week for three weeks. Tavares (1950) in Brazil finds this method much superior to arsenicals in 75 cases, and 40 were cured in an average of 27.12 days; average total dosage was 3 mega units. Spirochætes were not found six days after commencement of treatment. Penicillin aluminium monostearate (P.A.M.)

is the preparation recommended by W.H.O. (1953).

VI. Other antibiotics.—Chloromycetin (chloramphenicol) has proved satisfactory (Findlay and Ampofo). Aureomycin also is effective in cases resistant to penicillin (Lins, 1950) in doses of 0.75-1.5 grm. for 3-4 days in children. For adults 2 grm. is given daily for five consecutive days. Terramycin (Loughlin and Joseph, 1951) in the treatment of tertiary yaws is even more effective than procaine penicillin in the following dosage: 3 grm. on first; 2 grm. on second and third days (total 7 grm.). Sixty-five cases were observed for two months on terramycin by the mouth. Clinical cure is effected in 6-16 days. In over 80 per cent. spirochætes could not be demonstrated 48 hours after treatment had commenced. Wet secondary plantar lesions were healed in 11 days.

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Prophylaxis resolves itself into the adoption of measures to prevent contagion. These are the isolation and segregation of the affected; the dressing and treatment of wounds in the hitherto unaffected; the application of antiseptic ointments to yaws sores, so as to obviate the diffusion of spirochætes by flies; the purifying or destruction by fire of houses or huts notoriously infected; the prevention of pollution of bathing-water by yaws discharges; and, especially, the prompt treatment of the infected by salvarsan, bismuth, penicillin or terramycin.

CHAPTER XXXVI

MYCETOMA, BLASTOMYCOSIS AND OTHER FUNGOUS INFECTIONS

Synonyms.—Madura Foot; Pseudactinomycosis; Maduromycosis.

Definition.—A fungous disease of warm climates, affecting principally the foot, occasionally the hand, rarely the internal organs or other parts of the body. It is characterized by enlargement and deformity of the part; an oily degeneration and general fusion of the affected tissues. The disease runs a slow course, is never recovered from spontaneously, and, unless removed, terminates after many years in death from exhaustion.

Geographical distribution.—In India, mycetoma is endemic in widely scattered districts, although whole provinces, as that of Lower Bengal, enjoy an almost complete immunity. It appears to be acquired only in rural districts, the inhabitants of the towns being exempt. Among the more afflicted districts may be mentioned Madura—hence the name "Madura foot" by which mycetoma is often known—Delhi, various places in the Punjab, Kashmir and Rajputana. In recent years we have had accounts of its occurrence with some degree of frequency in Senegambia, Somaliland, Aden, Algeria, Egypt, the Sudan, Madagascar, Cochin-China, Italy, the United States, and South America.

Ætiology.—The following varieties have been described:—

i. ACTINOMYCOTIC MYCETOMA

Caused by the ray-fungus, Actinomyces bovis (Harz, 1877). Actinomycosis has a world-wide distribution and is a common disease of cattle. It destroys bone by erosion and spares only nerves and tendons. The pus from the affected region contains small yellowish granules ("sulphur grains") of irregular shape, attaining at most 0.75 mm. in diameter. They are soft and consist of an inextricable felted mass of mycelium. The threads are radially arranged at the periphery of the grain, and their free extremity widens into a bulbous, club-like termination (10–20 μ long by 8–10 μ wide). These clubbed ends have been looked upon by several authors as forms of degeneration.

ii. VINCENT'S WHITE MYCETOMA

Caused by Actinomyces maduræ (Vincent, 1894). This kind of mycetoma is common and widely distributed. It has been observed in Algeria, in Abyssinia, in Somaliland, in Cyprus, in India, in Argentina, and in Cuba.

Unlike A. bovis and other mycetoma-producing fungi it does not destroy bone, and does not seem to act directly on the general health of the patient, though ultimately and indirectly it may bring about cachexia.

iii. NICOLLE'S WHITE MYCETOMA

Caused by Aspergillus nidulans (Eidam, 1883). So far, only a few cases have been observed, by Nicolle and Pinoy, in Tunis, but probably it occurs in many places, the parasite A. nidulans being widely distributed. Primary infection probably takes place from barley grain. The grains formed by this fungus may also attain the size of a pea, but they differ from those of Actinomyces maduræ, inasmuch as they are more or less spherical and present a smooth surface.

iv. Bouffard's Black Mycetoma

Caused by Aspergillus bouffardi (Brumpt, 1906). The grains are quite characteristic. They are black and vary in size from a pin's head to that of No. 1 shot. They present a mulberry-like surface which is smooth and glossy, the structure consisting of a coiled-up mass. The fungus has not been cultivated.

V. CARTER'S BLACK MYCETOMA

Caused by Madurella mycetomi (Laveran, 1902). This mycetoma has a very wide distribution. It has been observed in Italy, in Africa (Senegal, French Sudan), and in India.

The grain formed by Madurella mycetomi is dark-brown or black. It measures 1 to 2 mm. in diameter, is hard and brittle; its surface is irregular and frequently presents pointed eminences which differentiate it from the larger and smooth grains of Aspergillus bouffardi. The grain is composed of white threads, always over 1 μ in diameter and attaining at times 8 to 10 μ , which secrete a dark-brown substance that cements them together.

VI. BRUMPT'S WHITE MYCETOMA

Caused by *Indiella mansoni* (Brumpt, 1906). This form was described from a specimen of Indian origin in the museum of the London School of Hygiene and Tropical Medicine.

The grains peculiar to this form are hard, white, and very small, varying in size between $\frac{1}{3}$ and $\frac{1}{4}$ mm., and having a lenticular shape. Some are bean-shaped and flat. To study their structure it is necessary to boil them first in a solution of caustic potash. The hyphal threads are large and closely set, but without any cementing substance between them. The periphery of the grain contains numerous large chlamydospores having thick walls and being full of protoplasm.

vii. REYNIER'S WHITE MYCETOMA

Caused by *Indiella reynieri* (Brumpt, 1906), originally described by Reynier from a specimen in Paris; a second case has been recorded from Greece.

The grains may attain 1 mm. in diameter; they are soft, white, and consist of a coiled-up strand which gives them a peculiar appearance resembling the excrement of earthworms.

viii. BOUFFARD'S WHITE MYCETOMA

Caused by Actinomyces somaliensis (Brumpt, 1906). Bouffard has found it twice in Somaliland, and it occurs in the Sudan and in South Africa.

A. somaliensis is a most destructive fungus. In a foot examined by Brumpt all the muscles, tendons, and bones had been replaced by sclerosed tissues, more or less homogeneous, presenting numerous sinuses full of yellowish grains clustered together like fish-roe, and many small inflammatory nodules containing one or more grains.

It is necessary to add that the numerous fungi which have been isolated fall into three classes: schizomycetes, ascomycetes and fungi imperfecti. In the former group several species of the genus Nocardia are found. These are the aërobic forms of actinomyces. In the second the genera Allescheria, Aspergillus and Penicillium are found and in the fungi imperfecti Madurella, Indiella, Cephalosporium, Monosporium and Glenospora.

Culture.—Cultures can be made, as in actinomycosis, both under aërobic and anaërobic conditions on glucose or glycerol-agar plates, in shake cultures or in Loeffler's serum. Some workers recommend keeping cultures in an atmosphere of CO₂. The medium should be inoculated directly with colonies from the

pus but, owing to slow growth of the actinomyces, pure cultures are somewhat difficult to obtain, unless the pus is free from contamination with other organisms.

Pathology.—On cutting into a mycetomatous foot or hand the knife passes readily through the mass, exposing a section with an oily, greasy surface, in which the anatomical elements in many places are unrecognizable, being, as it were, fused together, forming a pale, greyish-yellow mass. The bones have in parts entirely disappeared; where their remains can still be made out, the cancellated structure is very friable, thinned, opened out, and infiltrated with oleaginous material. Of all the structures, the tendons and fasciæ seem to be the most resistant.

The most remarkable feature revealed by section is a network of sinuses and communicating cyst-like cavities of various dimensions, from a mere speck to a



Fig. 104.—Mycetoma of about two years' standing. (After Legrain.)

cavity an inch or more in diameter. Sinuses and cysts are occupied by a material unlike anything else in human morbid anatomy. In the black varieties this material consists of a black or dark-brown, firm, friable substance which, in many places, stuffs the sinuses and cysts; manifestly it is from this that the black particles in the discharge are derived. In the white varieties the sinuses and cysts are also more or less filled with a white or yellowish roe-like substance, evidently an aggregation of particles identical with those escaping in the corresponding discharge. In the very rare red variety the colour of the accretions is red or pink.

Under the microscope the mycotic elements can be readily recognized in the concretions. In microscopic sections of the tissues, evidences of extensive degenerative changes, the result of a chronic inflammatory process, can be made out. An important feature is a sort of arteritis obliterans, or extensive proliferation of the endothelium of the arteries, and, according to Vincent, a thickening of the adventitia of the ressels as well as of the capillaries in the more affected areas.

Symptoms.—Mycetoma begins usually, though by no means invariably, on the sole of the foot. The first indication is the slow formation of a small, firm, rounded, somewhat hemispherical, slightly discoloured, painless swelling, perhaps about ½ in. in diameter. After a month or rather more, this swelling may soften and rupture, discharging a peculiar viscid, syrupylooking, oily, slightly purulent, sometimes blood-streaked fluid holding in suspension certain minute, rounded, greyish or yellowish particles, often compared to grains of fish-roe. In other examples of the disease the particles in the discharge are black, having the size and appearance of grains of coarse gunpowder. Sometimes these are aggregated into larger masses up to the size of a pea. In time, additional swellings, some of which break down and form similar sinuses, appear in the neighbourhood of the

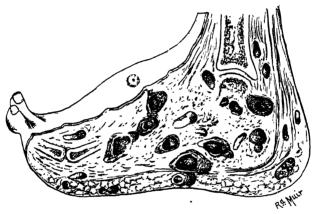


Fig. 105.—Section of a Madura foot. (T. R. Lewis.)

first, or elsewhere about the foot (Fig. 104). The sinuses are mostly permanent, healing up only in a very few instances. Gradually, the bulk of the foot increases to perhaps two or three times its normal volume (Fig. 105). There is comparatively little lengthening, but there is a general increase in thickness, so that in time the mass comes to assume an ovoid form, the sole becoming convex, the sides rounded and the anatomical points obliterated. The toes may be forced apart, bent upwards at the tarso-phalangeal joints, or otherwise misdirected, so that when the foot is placed on the ground the toes do not touch it. The surface of the skin is roughened by a number of larger or smaller, firmer or softer hemispherical elevations, in some of which the orifices of the numerous sinuses open.

The discharge from the sinuses differs in amount in different cases, and from time to time in the same case; whether profuse or scanty, it always exhibits the same oily, mucoid, slightly purulent appearance, and may stink abominably. With a very few exceptions it contains either the grey or the black grains, rarely reddish or pink ones.

As the foot enlarges, the leg atrophies from disuse; so that in the advanced disease an enormously enlarged and mis-shapen foot, flexed on

extended, is attached to an attenuated leg consisting of little more than skin and bone. In some cases the tibia or bones of the forearm are involved: in others the disease at first may be confined to a toe, or a finger, or other limited area. In a very few instances the seat of the disease is the knee, thigh, jaw, or neck. Unless the case be one of actinomycosis, the internal organs are never implicated, either primarily or secondarily. The lymphatic glands, likewise, although they may show adenitis from secondary septic infection, are very rarely involved.

After ten or twenty years the patient dies, worn out by the continued drain, or carried off more suddenly by diarrhoea or other intercurrent disease.

Treatment.—The only effective treatment is amputation, well above the seat of the disease; for the long bones may be implicated, as well as the small, and unless the entire disease be removed, it will recur in the stump. Complete removal is not followed by relapse. If a toe, or a small portion of the foot or hand, is alone involved, this may be excised. Potassium iodide in large doses has been found beneficial in certain forms.

Buchanan recommended surgical removal of as much diseased tissue as can be conveniently reached. Then tincture of iodine should be injected into any suspicious area remaining, in the hope that the surviving elements will be killed; therefore 1–2 ml. of tincture of iodine should be injected every ten days for at least two months. At first, the local reaction is not severe, but later it becomes so. Probably a less irritating solution, such as Lugol's, would be better.

Potassium iodide should be given by the mouth in large doses over a considerable period, and there are those who think that the French tincture of iodine is more effective, if administered in frequent doses of 2 drops in milk. Sulphonamides—sulphapyridine and sulphathiazole—in full doses have been found effective in Madura foot (Hollenbeck and Turnoff, 1943; Billington, 1944). The action of penicillin on actinomycosis has led to its application in Madura foot. Although genuine cures have been reported by Lehman, Herrel, Jones, Walker and Hamilton (1945) in doses of 1½–2 mega units, Dostrovsky and Sagher (1948) found that it had no action in their case. Streptomycin is probably better than penicillin, although data are lacking.

Chromoblastomycosis, "Mossy foot" (Fig. 106).—The name is misleading because the organisms do not form buds in tissue or culture. A papillomatous condition of the legs and feet first described by W. Thomas in the Amazon Valley, Brazil, but now reported from Honduras, North, East and South Africa, South America, Porto Rico, Southern United States, Dutch East Indies, Japan, South Russia, Rhodesia and Queensland.

The disease is caused by Phialophora verrucosa (Thaxter, 1915). The organism has also been named P. pedrosoi (syn. Hormodendrum pedrosoi), Fonsecca pedrosoi and P. compactum (syn. H. compactum). These fungi develop greyish-green to olive-green velutine colonies, becoming black and glabrous with age. P. verrucosa is characterized by spores borne on a flask-shaped cell (phialide) with a cup-shaped extremity, and the other two species by a hormodendrum-like sporiferous apparatus and sometimes by the form acrothecium. Species of Phialophora have been found growing saprophytically on forest timber.

The foot and ankles—usually of males engaged in agriculture—are covered

with warty outgrowths resembling barnacles, which are vascular and sometimes painful, a process which may take 15 years. They are usually papillomatous, but occasionally pedunculated. The sole of the foot usually escapes. It is claimed that the disease can be inoculated into the nose of rabbits, producing a verrucoid mass.

The diagnosis is established by demonstration in sections of a tuberculoid type of reaction with rounded brown bodies resembling yeast cells, which multiply by splitting, not by budding. The best treatment is actual cautery. Mossy



Fig. 106.—Chromoblastomycosis of feet in a European. (Dr. L. A. León, Quito, Ecuador.)

foot has to be distinguished from "lymphostatic verrucosis" described by Loewenthal and Manuwa (1935) from Uganda and Nigeria. This is a papillomatous condition of the soles of the feet, resembling minute mussels. The essential pathology is due to lymph statis, chronic cedema and hyperkeratosis.

Coccidioidomycosis is probably the most infectious of systemic mycoses and the majority of individuals who live in the endemic areas acquire the infection. The organism Coccidioides immitis appears as a non-budding, spherical thickwalled structure, $20-80~\mu$ in diameter, which is filled with numerous endospores (2–5 μ). In cultures the fungus reproduces by these endospores which are freed by rupture of the cell walls. The colonies are flat and greyish, with aerial hyphæ which are septate and branching with spherical arthropores. The disease occurs in South-West United States, in California, also in Texas, Arizona and

New Mexico. Only about six cases have been seen in South America, and a few from Hawaii, Italy and South-East Europe. It may result in (1) primary coccidioidomycosis, a benign, self-limited respiratory disease; (2) progressive, a chronic, malignant, disseminated disease, involving cutaneous, subcutaneous, visceral and osseous tissues (Fig. 107).

The greatest endemic focus is the San Joaquin Valley, where some six thousand cases in U.S. Army were diagnosed during the recent war, and skin tests have shown that 75 to 97 per cent. of children react positively to coccidioidin. Man acquires infection from an extraneous source, but it is found naturally in cattle, sheep and dogs. Possibly, rodents form a reservoir of infection.

In the primary preliminary form, "Valley or Desert Fever," the organisms are inhaled with dust. Many are subclinical. There is a pneumonic type of infiltration, accompanied by skin lesions resembling crythema multiforme or

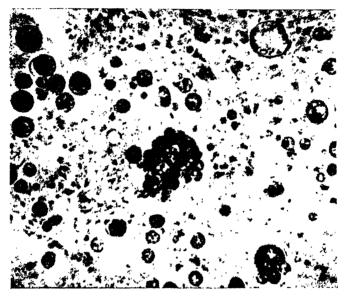


Fig. 107.—Coccidioides immitis in necrotic liver. (Dr. Oscar Felsenfeld, Chicago.)

erythema nodosum, with pronounced eosinophilia. In 80 per cent. changes in the lungs are demonstrated by X-rays as soft, fuzzy thickenings. Nodular lesions in the lung parenchyma measure 2–3 cm. in diameter.

Non-pulmonary primary coccidioidomycosis occurs on exposed surfaces and is known as coccidioidal granuloma, or Posada's disease, beginning as a solid nodule with pink or dusty red discolouration of the skin. The lesion ulcerates, exuding pus in which the organisms can be found. After a few weeks the nodules become papillomatous. The scrofulodermic type involves the superficial cervical glands. In progressive coccidioidomycosis it occurs in 0·2 per cent. of cases of primary infection and develops into fatal form. The symptoms and signs resemble chronic tuberculosis. Meningitis is found at autopsy in 25 per cent.

Treatment is expectant and the progress is excellent in primary cases, good in

the cutaneous, but bad in the internal and meningitic. In patients diagnosed by coccidioidin improvement is accelerated by potassium iodide.

North American Blastomycosis or Gilchrist's Disease.—Blastomyces dermatitidis appears in the tissues as a round, budding, yeast-like fungus and produces aerial hyphæ on Sabouraud's medium, which distinguishes it from cryptococcosis. Nearly all cases reported are in U.S.A., with a few in Canada and England. Natural infection has been found in dogs. There are two main types—systemic and cutaneous. The former commences in the lungs from inhalation infection and resembles tuberculosis. The latter causes ulcers of gummatous type on face, neck, hands, arms and feet. Bone infections occur in 60 per cent. and lesions of the C.N.S. in 30 per cent. In X-rays the striking feature is enlargement of the mediastinal glands.

Diagnosis is made from biopsy which shows extraordinary hypertrophy of the epidermis and from abscesses which show yeast-like organisms with double con-

tour, 8-15 μ in diameter.

There is also an intradermal test with injection of 0-1 ml. standardized heat-killed vaccine of B. dermatitidis. Treatment is with potassium iodide by the mouth in the systemic form and by sodium sulphapyridine injections in oily emulsion, or sodium propionate 10 per cent. in 25 per cent. propylalcohol. X-ray therapy is also useful, but dangerous if there is a co-existent underlying tuberculous focus.

South American Blastomycosis (Lutz—Splendore de Almeida Disease) (B. brasiliensis) is confined to South America. The fungus in tissues resembles B. dermatitidis, but is distinguished by its multiple budding forms. There is usually enlargement of lymphatic glands. (1) The cutaneous form is characterized by cutaneous and mucosal lesions, particularly in region of mouth and nose. (2) The lymphatic type. (3) The visceral form, with lesions in liver, spleen, etc. (4) Mixed type.

Diagnosis.—Complement-fixation tests have been perfected. B. brasiliensis (Paracoccidiodes brasiliensis) resembles fungi which belong to the class—Phycomycetes. Reproduction by simultaneous, multiple buds from all parts of its surface is a characteristic feature in parasitic life and in cultures vegetating in the yeast-like form at 37° C. (Mackinnon, 1949).

Treatment.—Lacaz (1950) has outlined the treatment which, he thinks, can be applied to all forms of blastomycosis. Sulphadiazine as suggested by Quiroga (1949) and de Barros (1950) is used in solid form to ensure slower absorption. The dosage, 1 grm. by mouth every six hours, with a blood level of 1-1 mgm. per 100 ml. suffices.

Combined sulphadiazine and sulphamerazine can be given in doses of 0.5 grm. each by mouth every 3-4 hours. In all cases chemotherapy must be supplemented by dietetic management and by specific vaccine therapy. The effects of sulphonamides is fungistatic, not fungicidal. The best results are obtained in cutaneous, mucous and pulmonary forms of the disease. Glandular types are more resistant.

Sporotrichosis.—This has been reported from Southern France, Southern U.S.A., South America, and South Africa, where it is common amongst the miners of Witwatersrand. It produces gumma-like swellings in limbs or trunk, which enlarge and ultimately break down, leaving deep ulcers, due to organisms, Sporotrichum (Rhinocladium) beurmanni, or S. schencki—which usually exist saprophytically—gain entrance to the body through an abrasion of the skin or esophagus. Occasionally they may be demonstrated in the blood; the

lymphatics, eye, oral cavity, periosteum, muscles, or viscera may become involved. In the discharges and tissues the parasites are scanty, so that the mycotic nature of the disease can only be made out from cultures. The lesions are granulomatous with epithelioid and giant cells. Individual cigar-shaped yeast-like parasitic elements are often found engulfed by phagocytes. Benham and Kesten isolated the organism from linear nodules in the arm, and reproduced theymphatic type of infection in a monkey. Inoculation of white rats produced typical orchitis. In man infection may be caused by a thorn prick or other injury.

Pijper and Pullinger (1927) recorded 14 cases in native miners on the South African Rand. They distinguished a primary sore in the form of a localized ulceration on a finger, or the shin. Ten of the fourteen cases had the lesions confined to one arm; the others were on the shin, with lesions extending as high as the buttock. Incision of the nodules in the paths of the lymphatics produced pus or serous fluid. More recently Du Toit has reported one outbreak in the Rand mines involving 650 cases in one mine shaft alone.

Sporotrichum beurmanni can be isolated from the tissues by aspiration and insemination on to Sabouraud's medium. The parasite occurs in wild rats in Argentina and Brazil, while a similar disease, apt to be mistaken for epizoötic lymphangitis, occurs in horses and mules in Madagascar (Carougeau).

It appears to be a common parasite in nature, and (1933) Benham and Kesten have transmitted the human parasite to carnations, in which it produces a "bud rot" similar to that caused by a natural parasite, S. pox. Potassium iodide in large doses is specific for this infection.

Hemisporosis (Hemispora stellata) is a disease like sporotrichosis reported from Italy, and is characterized by granulomatous growths resembling syphilis or tuberculosis. Occasionally bones are affected.

Torulosis (or cryptococcosis).—This gives rise to grave lesions of the pulmonary and nervous systems, and local tumours of a peculiar consistency containing round cells surrounded by a gelatinous substance secreted by the organism. It is found especially in California, but has also been reported from Europe, India, Australia, Japan, Canada, Central and South America. The parasite, which has been especially studied by Kessel, is known as Torulopsis histolytica or Cryptococcus neoformans. The yeast-like cells are usually found in the cerebrospinal fluid. Experimental infections are easily produced in rats and mice by intraperitoneal injection, generalized lesions being found in lungs, liver, spleen, The cutaneous form—"Busse-Buschke's disease" or kidneys and brain. "European blastomycosis"—may precede or follow systemic infection. It is characterized by acneiform lesions and subcutaneous nodules. In the generalized form there is invasion of the central nervous system, less often of the lungs, liver, spleen and joints, especially the knee, it closely simulates tuberculosis. This disease appears to be incurable. The diagnosis is usually made by cerebro-spinal puncture. The protein content and globulins are raised, as in other forms of meningitis; the sugar content is lowered and chlorides reduced. A localized rounded tumour, or toruloma, has been found in the cerebellum (Daniel and colleagues, 1949)1.

 $T.\ histolytica$ is a primitive form of yeast cell, thick-walled, 5–20 μ in diameter; it multiplies by gemmation, does not produce endospores or mycelium, and can be cultured in glucose broth or on Sabouraud's medium. The colonies are honey-coloured and semi-fluid in contrast to the glistening white colonies of Candida albicans (Monilia albicans), and show no mycelia penetrating into the

¹Two fatal cases are reported by Symmers (1953). The first in an ex-service man from Burma, resembling Hodgkin's disease. Death resulted from a hemorrhagic granuloma of the brain. The second was a woman, who lived in London.

substratum, as is characteristic of candida. The individual cells multiply by gemmation, no hyphæ being observed. The cells exhibit characteristic capsules. No asci are formed.

The sugar reactions are typical: no acid or gas is produced in arabinose, dextrose, galactose. inulin, maltose, mannitol, raffinose, sucrose, lactose or dextrin. The reaction in milk is alkaline. When it is inoculated intraperitoneally into rats and mice, the animals die in eight to twenty-eight days, and the organisms can be recovered from the tissues. Monkeys inoculated intracardially develop small nodules on the face, eyelids and ears, containing the organism. In some monkeys, however, a generalized torulosis of the brain and spinal cord develops. The fungus is widely distributed in nature and has been isolated from a number of plants and animals, from milk, as well as from the mouth and skin of healthy people, and is said to be susceptible to penicillin treatment.

Moniliasis is an infection with the ubiquitous thrush fungus, Candida albicans, which may infect the skin and deeper tissues, especially on the perireum and around the anus. It may produce also onychia and parenychia. Cutaneous infections are best treated with potassium permanganate or 2 per cent. mercurochrome.

Histoplasmosis (Reticulo-endothelial cytomycosis).—This was considered to be a rare disease, but is becoming increasingly important, and is reported from Central and South America, U.S.A., England, Philippines, Indonesia and South Africa. Darling (1906) first described it in Panama in a heavy pulmonary infection with a yeast-like organism, Histoplasma capsulatum, Cryptococcus capsulatus). It is primarily a disease of the reticulo-endothelium and the organism is rarely found extracellularly in tissue. Usually it produces a syndrome resembling kalaazar, which is always fatal. The organisms enter through the mouth and primary lesions on lips, tongue and larynx have been described. In a few cases cutaneous ulcers have been seen and enlargement of the lymph glands has been noted, as well as intestinal ulceration. Occasionally the first evidence is seen in a lymph gland. the knee-joint, or in one of the internal organs. Although the lungs are involved in about a quarter of 50 reported cases, pulmonary invasion occurs as part of the generalized disease. There is some evidence that the infection may be acquired from dogs, as the disease has been found in them, and they are susceptible in the laboratory. The majority of cases have so far been in children under thirteen years of age and the duration of the disease is three weeks to eight months; it may occur at any period from three months to eighty years. Radiography reveals enlarged hilar glands with peribronchial thickening and sometimes nodular lesions. The bone marrow is nearly always infected, resulting in a progressive hypochromic anæmia and leucopenia. The diagnosis is usually made by biopsy and the organisms are best seen in smears. They have to be distinguished from Leishmania donovani, appearing as small oval bodies in the mononuclear cells. The organism has been isolated from the pus of otitis media as well as from the knee-joint, endocardium and sputum (Bras). In the majority of cases there is emaciation, fever, anæmia, leucopenia, hepato- and splenomegaly. Derry, Gard and Wilson (1942) diagnosed this disease in a soldier from India and the Sudan who presented features resembling kala-azar, but with submental and inguinal abscesses. Duncan has reported on five cases of authentic histoplasmosis in England since 1941. In two there was no evidence of the infection having been contracted in this country; in three it was unquestionably tropical. The African species is separable by the presence of larger forms and is known as H. duboisii.

Recent work by Christie and Peterson appears to indicate that histoplasmosis in a benign form is very widely distributed, and closely resembles pulmonary tuberculosis. This has been effected by the use of an antigen—histoplasmin—

obtained from cultures of *H. capsulatum*. It is prepared from suspensions of the yeast form of the fungus in broth and, when injected intradermally, the reactions obtained are similar to those produced by tuberculin. From this it appears that pulmonary calcification in pulmonary histoplasmosis is twice as great amongst reactors to histoplasmin, as amongst those reacting to tuberculin.

The organism grows on Sabouraud's medium at room temperature and on blood agar at 37°C. On the former it produces white, cottony, aërial mycelium, turning later to buff brown. On the former there are dull white colonies consisting of yeast-like cells with fragments of mycelium. They may resemble colonies of Staphylococcus albus. Salvin has prepared from the yeast-like forms an antigen for complement-fixation known as "Y.P." An antibiotic from young tomato plants—tomatin—is said to be specific for cultures of H. capsulatum (Fontaine).

Lingua nigra, or black tongue, characterized by hypertrophy of the filiform papillæ, is due to Cryptococcus linguæ pilosæ, composed of yeast-like cells and mycelial elements, which can be cultured on maltose-agar. It is said to be

curable with nicotinic acid.

Section V.—DISEASES OF THE CENTRAL NERVOUS SYSTEM

CHAPTER XXXVII

NEURASTHENIA IN THE TROPICS

PSYCHONEUROSES play a considerable part in adding to the burdens of life, and are the cause of a proportion of invaliding among European officials and business men from the tropics; more especially from West Africa. As a cause of disability, neurasthenia or anxiety psychoneurosis, or whatever term may be applied to this real and distressing condition, has superseded tropical diseases. Therefore, from the point of view of Colonial Administration, neurasthenia is of greater importance than the majority of the tropical diseases with which this book deals. There is nothing peculiar to tropical neurasthenia which differentiates it from similar anxiety neuroses in temperate climates.

When it is considered that, in the figures quoted by Squires, no less than 45 per cent. of 353 invalidings of Europeans from the tropics were for psychological reasons, there is obviously some feature in life under tropical conditions which pre-disposes towards this state. Fully developed and frank neurasthenia, as seen in its most characteristic form, is more apt to develop in a neurotically-disposed individual than in one of a complacent and unemotional mental make-up, and it is not always possible to gauge with accuracy those individuals in whom tropical neurasthenia will eventually develop. Culpin pointed out that certain persons go to the tropics as a flight from the strain of social life at home.

In an analysis of neurasthenia in West Africa, Rowland Hill (1943) found that patients with long-standing conditions of nervous instability were made worse by tropical life, but in nearly all there was evidence that the neurasthenic tendency had been exaggerated by illness acquired in the tropics.

The influence of tropical infections.—Tropical infections, especially the enervating, debilitating, and irritating recurrent relapses of malaria, are predisposing factors. The recurrent headaches and fevers encourage patients to refer sensations to the cranium, so that they complain of neurasthenic headache, lack of concentration, loss of memory (West Coast Memory), and general disinterestedness in life. Intestinal infections, such as amoebic or bacillary dysentery, may promote concentration of thought on the intestinal tract. The patient's attention becomes rivetted on his digestive system, with the result that introspective psychoneurosis develops. In this respect tropical infections do undoubtedly predispose to "tropical neurasthenia." But there are other aspects of life in the tropics which engender introspection. The heat, the proximity to natives who cause annoyance and whose ways and psychology the European cannot understand, the dull monotony, the ever-recurring twelve hours of daylight alternating with twelve hours of pitchy night, and the abundant and vexatious insect life; all act as stimuli which goad to the neurasthenic

state. The dulling of the appetite engendered by heat, the unpalatable and unsuitable food, the greasy cooking, the abundance of starchy matter, the monotony of tinned foodstuffs, together with the comparative absence of essential vitamins, all tend to upset the digestive apparatus and to depress the higher psychical centres.

Fear of disease and hypochondriasis are sources of neurasthenia in previously healthy and well-balanced people who, after serving in the tropics for long periods, have suffered a good deal of illness without much deterioration, but with loss of confidence in their ability to stand tropical life. All those who have a tendency to anxiety neurosis are made worse by exposure to heat.

Sleep.—Insomnia, which is the outward manifestation of physical exhaustion, and which nearly always appears towards the end of the tour in tropical Africa, is usually the first manifestation of the neurasthenic state, and imperatively indicates invaliding to a temperate climate.

Sexual factors.—Other factors will occur to anyone who has lived in isolation under tropical conditions. There is the sex factor, which may be potent; there is the social isolation which operates in out-stations; in others it is excess of alcohol, late hours, or living an unaccustomed life attended by native servants—all these may upset the mental equilibrium. Then there is, too, the constant restraint and watchfulness required to avoid offending against local prejudices, and having to live with others who are also in a state of constant exasperation.

Work and exercise.—Probably hard mental and physical work, in moderation, act as a bar rather than as a predisposing factor in the development of neurasthenia. Mental occupation tends to divert the mind from self-interest. On the other hand, mental pressure or undue stress appears to be less easily tolerated in the tropics than at home. Neurasthenia is not a special affliction of Europeans, for it is frequently observed amongst the educated native officials in West Africa, Malaya and India, though the proportion is by no means so great as in Europeans.

Neurasthenia in women.—It is difficult to state the sex incidence of neurasthenics; probably women, with their more highly developed emotional centres, are more apt to develop it, granted equal opportunities, than men.

A tropical climate usually produces certain psychological effects in women. Those who become neurasthenic suffer from pelvic pain and discomfort, menorrhagia and toxemia. Constipation, by favouring pelvic congestion and inflammation, and uterine displacements, have also to be considered.

The effect of the tropical climate on the newly-arrived European woman is at first distinctly exhilarating. The appetite is increased and the heat does not oppress her at first as it does in succeeding years, and she has a feeling of well-being. Menstruation frequently stops for a season. The sense of well-being may be so real that risks are taken which more experienced residents avoid, such as eating unsuitable food. The long hours that European women spend in shaded houses during the heat of the day engender a feeling of lethargy, due to extra work thrown on the liver, and want of exercise.

Childbirth in European women in the tropics is apt to be more difficult and laborious than in temperate climates, due very probably to the conditions of life; but even among native women between 30 and 40 per cent. of deaths are directly or indirectly connected with parturition. Native women, as a rule, give birth with extraordinary ease, and only where they have departed from a natural mode of life, and are living in seclusion, is parturition difficult.

The effect of tropical conditions.—Tropical life may have a disturbing effect on the mentality of even the most healthy and balanced individual. After a year or more of constant exposure to heat and humidity, the hours of sleep become disturbed, and the nervous system more sensitive to external stimuli. Insomnia

may be precipitated by certain electrical conditions of the atmosphere, at present little understood, skin conditions, especially prickly heat, and possibly a hyperglycamia which Dutch investigators in Java ascribe to the climate. Otherwise healthy adults often appear "nervy" and "excitable," showing exaggerated reflexes and nervous twitchings of the face and limbs, with increased reflexes, directly they return to a temperate climate. In the minor states of disturbance the fears and stresses disappear the moment cool headwinds are encountered, and peaceful and refreshing sleep is enjoyed once more. But transference to his home climate does not immediately relieve a fully-developed neurasthenic of his fears; on the contrary, the hum and bustle around him may act as further stimuli.

Symptoms.—The very appearance of the individual betrays his mental state. He (or she) is emotional to a degree, so that any sympathetic reference to health may provoke a flood of tears. There are others in whom the most profound depression reigns, and who may display suicidal tendencies; these are usually associated with intractable insomnia.

The patient usually complains of a headache confined to the temporal or parietal portion of the cranium. There is a sense of increased intracranial pressure. Others experience a sinking feeling in the abdomen, indefinite abdominal pain, or flatulent dyspepsia. There is usually a mild tachycardia, or rather vasomotor instability, with a fall in blood-pressure and a diastolic pressure below 80. The reflexes are usually exaggerated, and there may be a false anklecionus with hyperhidrosis of the palms of the hands and of the feet.

It has been suggested that the main symptoms are to be ascribed to hyperthyroidism, but the Editor has been unable to find any evidence for this hypothesis. With this degree of nervous instability it is not surprising to find divergence of the pupils on accommodation (Mœbius' sign) which by some is considered to indicate hyperthyroidism.

Treatment.—The main principle in treatment is to remove the patient from his immediate surroundings to a temperate climate with congenial companions. Usually, on arriving in a cool climate, natural sleep sets in and fears and anxieties disappear. The neurasthenic state may be temporary. On the other hand the emotional and depressive states should be treated seriously and efforts should be made to discover some underlying infection. The Editor has on several occasions seen profound neurasthenic symptoms disappear after treatment of an underlying unsuspected malaria. If alcohol has been taken in excessive amount, it must be cut down, or prohibited altogether. Efforts should be made to divert the patient's attention from himself. Hobbies of all kinds should be encouraged and there is probably no occupation more restful and curative than fishing in Scotland or Ireland.

For insomnia, mild hypnotics should be prescribed, such as allonal, luminal, or medinal. Sleep may be induced by a hot bath or a cup of Ovaltine. As a general sedative a mixture of the following type may be prescribed, to be taken three times daily:

Prophylaxis.—As the main treatment of neurasthenia entails removal from immediate surroundings its prevention is difficult. Once marked neurasthenia has developed in a European in the tropics, he should be invalided to a temperate climate and his return becomes a matter for anxious consideration.

There are cases in which the patient quickly regains his mental equilibrium; but should the mental depression continue, in spite of the simple methods recommended, then permanent invaliding should be considered. The Editor is of opinion that a patient with well-marked tropical neurasthenia should never be permitted to return, otherwise the old symptoms will reassert themselves directly he arrives in his old haunts, so that after a few months he will be sent home again.

CHAPTER XXXVIII

ENCEPHALITIS JAPONICA, OTHER FORMS OF ENCEPHALITIS AND ANTERIOR POLIOMYELITIS

Synonym.—Japanese Type B encephalitis.

Japanese Type B encephalitis is an epidemic encephalomyelitis involving the brain and spinal cord; it is to be distinguished from epidemic encephalitis (encephalitis lethargica) by the absence of eye lesions and other features to be detailed later, and from the autumn encephalitis described by Smorodintseff as occurring in the autumn months in Eastern Siberia.

Epidemiology and geographical distribution.— Encephalitis japonica, as its name implies, is well known in Japan, where it apparently has occurred in epidemic waves since 1871. In 1928 Kaneko and Aoki made an intimate study of the disease and were able to differentiate it from encephalitis lethargica and to determine its identity with *Encephalitis B*. In 1924 a very severe epidemic occurred in Japan during a very hot and dry summer season, when 7,000 cases were recorded, with a mortality of nearly 60 per cent. This disease spreads rapidly, in a manner more nearly resembling poliomyelitis, more commonly and more severely attacking those over fifty years of age, in contrast to the relatively mild disease it produces in young people.

During recent years it has also appeared in China, and in the summer of 1938 there was an epidemic in Peking. Cases have also been recognized in Shanghai, Amoy and Tientsin. It is now known to have a much wider distribution than was at first believed. It has been diagnosed in Korea, Formosa, Ryokyu Islands, and in the maritime Krais. In Japan most of the cases occurred in children, but in Pacific Islands, such as Okinawa, it attacked American troops during the second world war. It appears to be endemic in natives of Okinawa. Neutralizing antibodies were found in the blood of Okinawan horses and goats, but not in chickens.

Ætiology.—Knowledge of the virus of epidemic encephalo-myelitis comes from Kobayashi, Takaki, Nishibe and Hayashi. Credit is due especially to the latter for his important researches on its transference to monkeys, in which it produces the same histopathological lesions as in man. In America, however, white mice have been found more susceptible than monkeys. Webster and Fite demonstrated that the virus, which is active in the blood and in the central nervous system in the early stages, can be inactivated by convalescent serum.

The transference of the virus from man to man is by mosquitoes. The following species transmit the virus and have been found infected in the field: Culex tritemiorhynchus, C. pipiens var. pallens and Aëdes togoi. Another Japanese aëdes, A. esonensis, readily transmits by biting, as do the following North American species: A. nigromaculis and A. lateralis. Culex pipiens and C. quinquefasciatus are also capable of transmitting by bite. In Okinawa, however, C. (fatigans) quinquefasciatus did not appear to be the vector. There is also an analogy with equine encephalomyelitis, which has been observed in horses as well as in man and which is transmitted in this manner. In Japan it occurs in the summer and autumn. Perdrau, by using hyperimmune sera, was able to demonstrate antigenic relationship between the virus of encephalitis japonica and that of St. Louis. The dimensions of the virus particles are estimated as between 20 and 30 $m\mu$. This virus may be transmitted by blood transfusion.

Symptomatology.—The prodromal symptoms commonly encountered are headache, dizziness, sluggishness, and vomiting. These are followed by psychical

disturbances, very often by delusions, but in very severe cases coma ensues, ending in death. The psychical signs and symptoms may be entirely absent in the mild cases, and (in contrast with encephalitis lethargica) meningeal symptoms may predominate. Disturbances of the motor system are characteristic: there are clonic contractions of the muscles which may end in actual convulsions. Fine tremors of individual groups of muscles alternate with attacks of shivering and at he toid movements. The whole muscular tone is increased in the extremities and in the neck and face, especially the masseter muscles, which results in an anxious expression, and ends in trismus making mastication impossible. In very advanced cases, encephalomyelitis causes paralysis of the spinal cord, but, in direct contrast to encephalitis lethargica, eye symptoms are absent; nor is post-encephalitic Parkinsonism ever observed, though bulbar symptoms, resulting in failure of speech and difficulty in swallowing, are quite common and, in addition, defects in co-ordination and sometimes even cerebellar disturbances. Anomalies of superficial and deep tendon reflexes are usually present, especially in spastic cases. Salivation and excessive sweating are absent.

The foregoing description covers only the main features, however; actually the clinical picture is a many-sided one. There is also another aspect to this disease in that, though the neurological side dominates the picture, there is a secondary affection of the hæmopoietic organs, resulting in a secondary anæmia, which appears to indicate a generalized infection, rather than a local affection of the central nervous system. As a rule, the temperature chart is not characteristic, and the course is afebrile. There are cases, however, in which fever is noted for five to ten days, and these are followed by sequelæ, such as profound neurasthenia. The fulminating cases, which are fatal in twenty-four to forty-eight hours, are generally pyrexial. It is to be noted that there are no pupillary or eye symptoms, and there is no special affection of the bladder or bowels. Usually there is at first retention, followed later by incontinence.

Diagnosis.—The main points in differentiation from encephalitis lethargica have been noted. The cerebro-spinal fluid shows all grades of inflammatory disturbance. Kaneko and Aoki have shown that there is an increase of the albumin content from 9 to 350 mgm. per cent. A mouse-protection test or a complement-fixation reaction can be used for diagnosis. Differential diagnosis has to be made from lymphocytic choriomeningitis.

Pathology.—Epidemic encephalomyelitis is characterized by diffuse lesions in the brain and spinal cord: these take the form of small white knob-like aggregations of cells, composed of microglia intermingled with lymphocytes and leucocytes. Here and there ganglion cells are also found acutely damaged.

Treatment.—No specific treatment is at present known, but a vaccine made from formolized mouse brain has been used by Sabin for the immunization of American troops and exposed natives. More than 300,000 persons have been given two to three doses of mouse-brain vaccine. The virus has been adapted to eggs.

MURRAY VALLEY ENCEPHALITIS

In 1951 an encephalitis allied to, if not identical with, Japanese B. virus, broke out in the Murray Valley and N. Victoria in New South Wales. There were 40 severe cases and 17 deaths. Three strains of virus were isolated from the brain by inoculating the chorio-allantoic membrane of fertile hens' eggs. After several egg-passages it was possible to infect mice intracerebrally. Guinea-pigs and rabbits are refractory, though they developed neutralizing antibodies and

gave a positive complement fixation. The clinical picture was clear cut. Headache, fever and drowsiness were followed by a disordered consciousness. Stiffneck and involuntary movements, with upper and lower neurone paralysis, were followed by coma and death.

The cerebrospinal fluid showed pleocytosis with predominantly lymphocytic exudate. The brain was generally involved with necrosis of neurones, par-

ticularly the thalamus and brain stem.

In retrospect it is now thought to be the same as the Australian X disease of 1917–1918. In the sera of wild birds in the Murray Valley there is a high incidence of antibodies as in the case of equine and St. Louis encephalitis in U.S.A. Horses and dogs (not sheep or cattle) also give evidence of infection. The existence of a bird-mite reservoir has been substantiated in America and the human infection denotes a spill-over of virus from its natural avian habitat.

RUSSIAN SPRING-SUMMER ENCEPHALITIS

A somewhat similar, widespread and fatal form of encephalitis has been described and investigated by Pawlowsky and his Russian colleagues in Mongolia and Far Eastern territories in the scrubby wastes (Taiga country). It also occurs in the Urals, Karelia, the Eastern Ukraine and White Russia in thickly wooded valleys and in areas where reafforestation is being carried out. This disease has distinct seasonal incidence, and 80 per cent. of cases occur in May and June.

Ætiology.—This form of encephalitis has been shown to be due to a filterable virus transmitted by the bite of a tick (Ixodes persulcatus), in which the virus persists, as it is found infective in wild districts uninhabited by man. The virus has been isolated from the brains of various species of wild animals indigenous to the country, Eutamias asiaticus orientalis, Evotomys rufocamus arsenjevi, Microtus michnoi pelliceus and Cricetulus furunculus; these therefore constitute a reservoir of infection. Seasonal incidence of the disease during May and June corresponds with maximum prevalence of Ixodes persulcatus. The infection transmitted by bite of the tick is hereditary, and therefore larvæ and nymphs are also infective.

Symptomatology.—This form of encephalitis has an abrupt onset and runs a severe course with steep rise of temperature, severe headache, and vomiting. Symptoms of meningeal involvement are followed by signs of focal lesions in the central nervous system, paresis and paralysis of upper or lower limbs or muscles of the neck or back. Parkinsonism never occurs. The case mortality is about 30 per cent.

The virus can be grown in tissue culture or in developing chick embryo. A formolized vaccine is of prophylactic value. Russian observers claim good results from immune serum given very early in the disease: 10-15 ml. of serum are injected into the spinal canal and 30-50 ml. intramuscularly; this intramuscular injection is repeated two or three times at intervals of 24 hours.

The disease is quite distinct from louping ill transmitted by *Ixodes ricinus* in Great Britain and from Colorado Tick Fever in the United States of America. It does not appear to be related to tick-borne fever of sheep or to the Russian autumn encephalitis of Siberia.

ST. LOUIS ENCEPHALITIS AND EQUINE ENCEPHALOMYELITIS

St. Louis encephalitis is due to a filterable virus (Webster and Fite) which is allied to Japanese B. encephalitis and to the West Nile form. The path of invasion appears to be from the nasopharynx by way of the olfactory nerve apparatus. It appeared in epidemic form in St. Louis in 1933 with a case mortality of 20 per cent. The virus particles measure $20-30 \ m\mu$ and it has been

cultured on the chorio-allantoic membrane of the chick embryo. The virus is transmissible to monkeys in which it produces changes in the brain similar to those of man and also to mice by intracerebral inoculation. There appears to be strong evidence that the mosquito (Culex tarsalis) can transmit the infection (Hammon and colleagues). Equine encephalomyelitis is epidemic in horses and resembles the Borna disease of Europe. It has been recognized in U.S.A., Canada and South America, but it differs from the latter in the histological structure of the lesions and in the type of the virus. The epidemics occur in late summer and autumn. There are two types: the Western in river valleys, and the Eastern in salt marshes in Louisiana. The former is transmitted by Culex tarsalis, especially in Argentina, the latter by Aëles ægypti.

In 1937 there was a large outbreak which caused the death of thousands of horses and at the same time a considerable mortality amongst pigeons and pheasants. Cases in man have been recognized, especially in Venezuela, where several fatal cases have been reported, and which appears to be a different type. The virus from the Eastern and Western types can be grown on chorio-allantoic

membrane of chick embryo.

ACUTE ANTERIOR POLIOMYELITIS

Synonym.—Infantile Paralysis.

Epidemiology and geographical distribution.—As an endemic infection poliomyelitis has been found all over the world. In epidemic form it has been reported from N. America, Scandinavia and Australia. In the second World War serious outbreaks occurred in Malta, St. Helena, Mauritius and N. Africa, but the highest incidence in British troops was in India and in the Middle East. In Central and S. America outbreaks have been recorded in Argentina, Brazil, Colombia, Costa Rica, Ecuador San Salvador, Mexico, Nicaragua, Panama, Porto Rico, Uruguay and Venezuela. In the West Indies it is endemic in Barbados, Jamaica, Tobago and Trinidad. In Great Britain the average number of poliomyelitis and polio-encephalitis cases is about 1,000 annually. It is endemic on N. African seaboard, in Egypt, Palestine and Malta.

In Central Africa it is reported from the Congo, French Equatorial Africa and W. Africa, especially in the rainy season. In E. Africa it is found in Kenya, Tanganyika and Uganda, and also in the Union of S. Africa, St. Helena and Mauritius. It is endemic in India, especially in children; and in Japan, China, Indochina, Malaya (as in Singapore 1945–1946). In Australia epidemics have

been reported as well as in New Zealand.

Age and race incidence.—Outbreaks have affected predominantly those under 5 years of age. Hence the term "infantile paralysis." Those in warm climates are held to represent an epidemic "flare up" of an endemic infection. A noticeable feature of urban poliomyelitis during the last 30 years in the U.S.A., Australia and Scandinavia, has been the greater tendency to involve school children, as opposed to the pre-school child, thus resembling measles and diphtheria. Adults are not commonly attacked.

Race.—Certain coloured races seem to be lesss usceptible than white people. In the U.S.A. the reported incidence of the latter is 3-4 times as great as that in coloured people. In 1945 in Mauritius the Chinese showed the highest incidence. In Malta cases occurred in British troops, but not in the Maltese.

Other considerations.—Many observers have referred to a higher incidence in country districts than in towns and cities. There is a tendency for cases to occur predominantly in summer and autumn in the N. hemisphere and in the first four months of the year in the S. hemisphere. In recent years contact in the home seems to play an important part in the distribution of poliomyelitis.

Familial infections are commoner when exposed children are young than when they are over 10. As the virus occurs in fæces it is possible that it can gain access to water supplies, so that polluted water has been found to be responsible for infection of sporadic cases in U.S.A., whilst a number of outbreaks have been definitely traced to milk.

Ætiology.—The poliomyelitis group of viruses are composed of the most minute particles yet discovered.

The terms—human, murine and poreine types—have been proposed by Gard (1943). The bulk of the strains are transmissible to monkeys and chimpanzees, but cannot be adapted to rodents. One of the most important is the Lansing strain of Armstrong isolated in monkeys in 1939. SK strain of Jungeblut and Sanders was isolated from the fæces of abortive cases by monkey inoculation. This is adapted for mice and has lost its virulence for monkeys. M.E.F.1 strain was isolated in rhesus monkeys and infects cotton rats and mice. The M.M. strain of Jungeblut and Dalldorf (1943), causing paralysis of albino mice, cotton rats and hamsters, originated from the brain of a mouse.

Antigenic relationships in the poliomyelitis group.—Antigenic differences have been noted between freshly isolated human strains of the virus and those passed for some time in monkeys. Freshly isolated human strains also vary from one to another, but S.K., M.M. and Lansing strains are related. After inoculation by any route, monkeys and chimpanzees may suffer from non-paralytic attacks, but recover before paralysis sets in. The virus has not been detected in blood or urine, but has been frequently isolated from nasopharyngeal mucosa as well as in tonsils and adenoids, and it may persist for two weeks. The virus has been found in the fæces two days after onset and probably all cases excrete it during the first week and may continue to do so for 50 days.

Carriers.—It is now clear that the virus is widely distributed in the environment of abortive or paralytic cases. Whilst some contacts develop the abortive type, the majority are in good health, but carry the virus for the same length of time as do sufferers from poliomyelitis. The majority of positive isolations have been from children. Even infant contacts may be healthy carriers. Persons harbouring the virus in the nasopharynx may later develop poliomyelitis.

Clinical pathology.—Examination of the cerebrospinal fluid is important, especially in the preparalytic stage. The fluid is usually under increased pressure and hazy. There is an increase in cell count but the greater number of cells is to be found in the first week after the onset of paralysis. There are seldom over 100 cells per cmm., composed mostly of lymphocytes, but in the early stages polymorphonuclears may constitute 50 per cent. of the total. The total protein becomes increased, reaching its maximum in the third week. The colloidal gold curve is of the luetic or meningitic type.

Fehlings solution is always reduced, but there is no significant change in the chloride content. There is a blood leucocytosis up to 25,000 per cmm. in the paralytic stage and there is usually a 15 per cent. increase in the polymorphonuclears.

Acute anterior poliomyelitis in man.—Wickman's work on epidemiology (1907) suggested that the disease was infective. It soon became apparent largely by the work of Flexner in America that the pathogenic agent was a filterable virus. In a large number of cases bulbar or bulbo-spinal poliomyelitis has developed within 7–30 days of tonsillectomy or adenoidectomy. Tooth extraction may precipitate an attack and there is little doubt that pregnancy predisposes to it. Incubation period is 7–10 days with 3–20 days as outside limits.

Illness and infection.—There may be a transient minor illness at about the time of the presumptive date of infection. This is characterized by nasopharyngitis, fever and headache. After 1-2 days the patient recovers and appears well for 4-7 days when fever returns and paralysis supervenes. This is termed "dromedary" type of illness. In any epidemic there are likely to be several times as many non-paralytic as paralytic cases, especially in those under 16. Diagnosis of poliomyelitis in the preparalytic stage is difficult.

Preparalytic poliomyelitis begins in various ways and fever is usually present for 1-4 days. Catarrhal symptoms are common with sore throat, tonsillitis and nasopharyngitis. Frontal headache is frequent, but in other groups the onset

may be accompanied by gastro-intestinal symptoms.

Pain is elicited by any effort involving movements of the spine. Stiffness in neck and back and resistance to anterior flexion are common. These can be tested by pulling forward the head of the child, who then complains of pain, and rigidity is experienced by the observer; but when the shoulders are raised, the head usually falls back to the bed. Amoss', or the "tripod sign" is elicited by asking the child to sit straight up in bed, when he will place his hands on the bed behind himself for support. Kernig's sign is often weakly positive—muscular tremors, when present, usually heralding the site of forthcoming paralysis. The child is usually irritable and restless, but apathy and stupor may occur together in some and there may be encephalitic symptoms.

What are known as Phase I symptoms are thought to be due to involvement of the brain stem and basal nuclei. The patient may be drowsy, listless, restless or irritable. The sleep rhythm may be inverted. Even at this stage there may be changes in the C.S.F. Some cases may not develop any further. In Phase II the thalamic and hypothalamic disturbances persist. The virus spreads nearer to the cord and symptoms develop owing to involvement of the posterior columns. The neck is stiff and rigid. There is muscular ataxia and tremor whilst reflexes are increased. Pains may be spontaneous and are due to the involvement of the posterior columns and root ganglia: not to meningeal irritation.

Paralytic poliornyelitis.—The commonest types are the ordinary or spinal, the polio-encephalitic and the bulbar and bulbo-spinal types: cranial nerve paralysis has been noted more commonly in some outbreaks. Paralysis is flaccid, but the distribution is often asymmetrical, for instance one leg and the opposite arm; the cutaneous sensation is normal, the reflexes are absent in the affected limbs. The sphincters are unaffected. Recovery of movement may continue for three months. One leg is most commonly affected and next one leg and one arm. In lower extremities extensors of hip, knee and dorsi flexors of ankle are most affected, and in upper extremities the muscles of the shoulders. The abdominal muscles are but uncommonly affected in young children. During the stage of recovery permanent results become obvious, such as shortening of the affected limb, and deformities, such as talipes, flexed knees and occasionally scoliosis and lordosis.

Diagnosis.—The cerebrospinal fluid should be examined for cell count and estimation of protein. If the case is fatal, part of the cord should be retained for histological examination and the remainder should be placed in 50 per cent. glycerol for subsequent monkey inoculation. During convalescence the serum may be examined for the virus (neutralization test).

Differential diagnosis is important. Abortive poliomyelitis may resemble serous and lymphocytic choriomeningitis, simple infections of the upper respiratory tract, sandfly, dengue and dengue-like fevers. Many children diagnosed as "meningismus" are in reality abortive poliomyelitis.

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Prophylaxis.—Notification is practised in almost all countries and non-paralytic cases should be as fully reported as paralytic ones. Patients in whom the disease is either abortive or paralytic are isolated for three weeks.

During the epidemic periods gatherings of children should be forbidden. In rural areas schools must be closed, but in urban areas it is doubtful whether school closure is of any value. Water supplies must be chlorinated. Urine, feeces, and soiled linen must be sterilized by carbolization. Bathing in streams, lakes or even in chlorinated water in baths, must be forbidden.

CHAPTER XXXIX

LÂTAH, RUNNING ÂMOK AND KORO

Latah, a word signifying "nervous" or "ticklish," is not uncommon in the natives of the Malay Peninsula, Java, and the neighbouring islands. It occurs more frequently in women, especially young women, than in men; children are seldom affected; it rarely appears before puberty and is especially common at the menopause.

A somewhat similar affliction is described among the Ainu people, usually in women, and is known as *imu*. This manifests as psycho-motor attacks precipitated by some emotional shock. If a sufferer is startled, she may continue to echo everything that is said to her.

Lâtah persists for years. The main characteristics of this state are the same, though there is considerable variety in the intensity of the symptoms. The condition is incurable, shows no tendency to become worse, and does not terminate in insanity.

As the Malays say, an orang lâtah never becomes an orang gila (âmok). The subjects of "latah" at first appear to differ in no way from their neighbours and relations, but on some sudden and striking impression, such as a loud sound, or in response to some overt suggestion by word or deed, they pass into a peculiar mental state in which they involuntarily utter certain sounds and execute certain movements. In other instances they will imitate words or movements, or yield to suggestions from others. During this hypnotic-like state, which may last for a few minutes or longer, the victim is at the mercy of his prompter and will unerringly follow any lead indicated. Although the manifestations of high degrees of lâtah may be followed by exhaustion, or even by swooning, as a rule nothing of the kind occurs. The infirmity is usually discovered by accident. Swettenham, for instance, used to relate that it was only necessary for anyone to attract the attention of these men by the simplest means, such as holding up a finger, or calling them by name in a pointed way, touching them, or looking them steadfastly in the face, in order to make them lose control of themselves and be willing to execute whatever was suggested by a sign. On one occasion, one of them, on being told that a roll of matting was his wife, embraced it with every sign of affection; but when the other latah subject, a policeman, was convinced that the same roll was his wife likewise, he too embraced it, and the two men fell to the ground struggling for the possession of the "lady."

Lâtah folk are favourite subjects for the practical joker, and in a few instances they very much object to being made a show of, and may become dangerous. Lâtah seems to be akin to certain emotional stresses which are common in all barbarous and semi-civilized countries.

Abraham has seen the afflicted, if suddenly startled, fall down and imitate the gestures of anyone in sight; for instance, an old lady startled by a bicycle bell, will instantly imitate the pedalling of the cyclist till exhausted.

The most profound study of the pathodynamics of latah from the modern psychological aspects has been published by Yap (1952). From this it appears that latah reaction is related to "sleep intoxication" and the so-called "startled neurosis," and is to be differentiated from convulsive tics or "primitive hysteria." A special modifying of personality and the organization of fear in persons belonging to cultures of low technological level are suggested. He has drawn attention to the resemblance of latah to the "jumpers" or "shakers,"

a group of religious people, originating from the Methodist congregation of Wales during the time of the evangelist, Whitefield. They practised ritualistic jumping

and shaking to the accompaniment of incoherent gutturals.

Unless unforeseen accidents occur, lâtah is not fatal. Gimlette and others have called attention to the medico-legal aspects of the disease. Fortunately, examples in which lâtah has been shown to play a part in crime are rare. Temperamentally, all the Malay races are very highly strung and nervous, although externally impassive, and there appears to be an hereditary tendency to the lâtah state in every Malay.

Young-dah-hte is a state closely related to lâtah. Mongolian races are predisposed. Heredity does not seem to play any part. It differs from lâtah in that the patient continuously remains in the imitative condition and is always liable to reactions.

Nat-win-de is a religious dance with closed eyes and swinging movements. It is started by professionals and taken up by others.

There appears to be a somewhat similar affection amongst the Samoyedes which is known as "Ikota," and it is believed that the curious epidemics of religious ecstasy, which swept over Europe during the Middle Ages, were of similar origin.

Mirzachi is a hypnagogic intoxication seen in Siberia and has been compared

to "Schlaftrunkenheit" and is practically the same as Ikota.

Banga is a hysterical affliction in Congo women at puberty. The subject is convulsed and rushes about uttering wild cries.

"Amok" (or running amok) is a term used somewhat loosely for a condition which, in the fully developed form, drives its victims to blind fury and to kill without reason.

Usually the "amok" runner (or amoker) has a grievance upon which he allows himself to brood, and after a period of sullenness decides to kill the suspected person and at the same time to destroy as many other people as possible. He therefore arms himself, runs "amok," and buries his kris, when out to slay, in friend and foe alike, with the expectation of being killed in turn.

In other cases there may be premonitory signs in which a person mutters and has delusions. Quite suddenly he will run "âmok" and after the attack may fall into a deep slumber and become comatose. The liability to "âmok" attacks is greatest in the Malays and their drugs, such as Indian hemp (Cannabis indica), are known to be potent predisposing causes of the attack. Van Loon found that in Java "âmok" runners are often suffering from some infectious disease, and that the symptoms are hallucinations and confusion; such patients are impelled to flight and attack as reactions to imaginary dangers and the agony and terror caused thereby.

"Koro" occurs amongst the Macassars and the Buginese in Celebes, and is also well known among the Chinese as Shook Jong, originally described by Blonk in 1895. The term signifies "shrivelling," and a feeling occurs at regular intervals of the penis retracting into the abdomen; if help is not forthcoming the patient dies. In his anxiety, the patient grasps the penis, and if unable to do so, obtains assistance from others. It may be days before the attack subsides, and the sufferer cannot bear to be left alone. If help be not to hand, he will actually tie the penis to his leg with string, anchor it by means of a pin, or may even employ a double-bladed clasping instrument known as li teng hok, which is used by jewellers. By the native this tendency is regarded as the "Yin" principle, representing the female power, dominating the "Yang" principle, which

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represents the male element. In order that a "Yin" disease may be cured, a "Yang" medicine must be employed. The sufferers are generally neurotics, and the anxiety arises out of sexual conflicts. Various pathological conditions, such as ædema of the lower abdomen, hernia, hydrocele and elephantiasis of the scrotum, may evoke fear of an attack. An analogous state, characterized by diminution of the genital labia and shrinkage of the breasts, is known to occur in women.

Section VI.—TROPICAL VENEREAL DISEASES

CHAPTER XL

LYMPHOGRANULOMA VENEREUM

Synonyms.—Climatic bubo; Lymphopathia venereum; Esthiomène; Lymphogranuloma inguinale; Inguinal poradenitis; Poradenolymphitis; Nicolas-Favre disease (French).

Definition.—A generalized virus infection usually transmitted by venereal infection and associated with a self-healing primary sore and changes in the lymph nodes draining the area where the primary sore is situated. In addition to these lesions the virus may give rise to a genitoano-rectal syndrome with inflammatory stricture of the rectum, to meningo-encephalitis and to eye-lesions.

Epidemiology and geographical distribution.—Scheube originally applied the term "climatic bubo" to a type of adenitis terminating in suppuration, not uncommon in tropical countries. Whether it is becoming increasingly frequent, or whether because attention has been drawn to its peculiar nature in recent years is a moot point, but recently "lymphogranuloma" has emerged from the obscure recesses of textbooks on tropical medicine into the full limelight of general medicine, so as to merit the title of the "Sixth Venereal Disease," which has been bestowed upon it by Stannus.

In tropical practice the disease is found especially among negroes of both sexes, both in West Africa and in North and South America. It is found, however, in seaports throughout the world.

In 1913, Durand, Nicolas, and Favre described it in France, and possibly

the condition long known as the "strumous bubo" is the same.

In 1933 Stannus and Findlay described an indigenous case in England. Since then the Editor has seen several more, and recently Anwyl Davies discovered three. Now numerous reports of its occurrence in Italy, Rumania, Scandinavia, and in fact the whole of Europe, are to hand. At certain times and places it appears almost to be epidemic. There seems to be no doubt, that, in almost every instance, infection is acquired by sexual intercourse, normal or abnormal.

Ætiology.—Hellerström and Wassén (1980) originally transmitted the virus obtained from the pus of inguinal buboes to monkeys, intracerebral inoculation producing meningo-encephalitis. The virus, which is apparently contained in the leucocytes, consists of minute particles which can be easily seen, and were figured by Findlay (1989). They can be stained by Victoria blue, Giemsa or Casteneda's method; with Giemsa, the larger bodies take on a bluish-purple tint, while with Castañeda's stain they are reddish-purple. Larger and smaller forms of the virus particles can be demonstrated outside the cells, lying close to cell débris, in compact colony-like masses. When they are within cells the elementary bodies

may be found in the cytoplasm of either mononuclear or polymorphonuclear leucocytes. Occasionally, these groups may attain considerable size, forming cyst-like spaces; later, the cyst-wall may rupture. The larger forms have been observed in considerable numbers, chiefly within twenty-four hours of intracerebral inoculation. There therefore appears to be a development cycle of the virus which is complete in forty-eight hours. The virus particles, or granules, were first described in cells from inguinal buboes by Gay and Prieto in 1927, and similar bodies were found by Findlay in 1933. Miyagawa (1938) finally concluded that they represented the virus and gave their measurements as 0-125–0-175 μ, while Findlay, Mackenzie and MacCallum showed that they resemble similar bodies found in psittacosis by Bedson and Bland in 1932, larger morula-like particles breaking up to form the small virus or elementary bodies.

Intraglandular injection of guinea-pigs with the virus produces an inguinal bubo in almost every case, so that this method may be employed for diagnosis. The most reliable methods at present are Findlay's intracerebral inoculation of white mice, which produces encephalitis, and inoculation into the yolk sac of mice. Miyagawa found that a chipmunk, Tamias asiaticus, is highly susceptible to intratesticular and intracerebral inoculation. The virus can also be cultivated on chick chorio-allantoic membrane in tissue culture. Ravaut, Levaditi, Lambling, and Cachera devised a method of isolating the virus from ulcerative proctitis by inserting a portion of tissue under the skin of a guinea-pig. After a few days, the inguinal gland is excised, emulsified and injected intracerebrally into a monkey. In inoculated mice a characteristic train of symptoms is evolved in five to seventy days, in which weakness, paresis, opisthotonos and convulsions occur. The concentration of the virus in the injected mouse brain is not great, so that dilutions greater than 1 in 1,000 fail to give positive results.

A protection test has been devised, by mixing equal parts of serum of the lymphogranuloma patient with an emulsion of infected mouse brain, diluted 1 in 5 in normal saline, and kept for the night in the ice-chest at 4° C. Doses of 0.5 ml. injected intracerebrally do not produce encephalitis. The serum of monkeys which have recovered gives the same reaction.

Pathology.—The essential features of the pathology of the human gland consists in little pin-point epithelioid formations scattered all through the gland substance. They are made up of masses of irregularly disposed macrophage cells together with some giant cells. Höppli described localized collections of eosinophils. Subsequently tiny micro- or stellate abscesses form.

Symptoms. Primary sore.—Durand in 1913, and subsequently Hanschell, described a small herpetiform ulcer on the prepuce which heals in a few days; the adenitis proper does not commence until after the primary lesion has healed. Hanschell believes that the disease does not usually occur in the circumcised. The primary lesion is an erosion with clean edges, and is surrounded by a reddened zone, but with only slight infiltration and induration. The base of the ulcer is usually whitish-grey.

Adenitis.—The incubation period of adenitis is three to four weeks after coitus, but it may be as long as six weeks to two months. The disease generally commences with remittent pyrexia, which may precede the actual localizing signs, and may be mistaken for typhoid. Soon, subacute inflammatory

swellings of the groin glands are noted. The inflammation may be unilateral or bilateral; while the oblique glands are most frequently affected; at times the crural glands are attacked. Sometimes one groin is affected after the other. In well-marked cases, the internal iliac glands, sometimes the lumbar glands also, can be felt enlarged and tender on deep palpation. Signs of intoxication from absorption may be widespread, producing prolonged intermittent or remittent fevers, sometimes even pyrexia of 103–5° F. Rigors, vomiting, cyanosis, even slight jaundice, and considerable pain have been noted. Rheumatic-like pains in joints and painful effusions into joint cavities may also occur as a result of absorption. The affected glands slowly enlarge to the size of a hen's egg, or even larger, and after several weeks, it may be months, the swelling gradually subsides (Fig. 108). Usually, the periglandular connective tissues inflame, and the



Fig. 108.—Fully developed climatic bubo in right groin, showing also small primary lesion on the corona penis. (A. H. Walters.)

integuments become adherent until suppuration ceases. At other times fistulous tracks form, and continuously exude a clear sticky fluid. The most striking clinical feature in the male is the extensive inflammation of the periglandular tissues with comparatively little pain and suppuration. The following stages are recognized:—

(1) A firm solitary gland, with no apparent causative lesion other than a recently-healed ulcer on the genitalia.

(2) Å firm solitary gland adherent to overlying skin and deeper tissues. Adjacent glands are enlarged, including external iliac glands, palpable as a mass above Poupart's ligament. The affected glands tend to coalesce.

(3) The glands in the groin soften and fluctuate. If incised, a cavity is disclosed, trabeculated by coarse, fibrous strands.

(4) The softened gland-mass ulcerates through the skin, and spontaneous fistulation occurs. Secondary infection follows.

It was formerly believed that lymphogranulomatous adenitis was unknown in women (Hanschell, 1926), but it is now becoming recognized that typical inguinal poradenitis does occur, though inguinal bubonic manifestations are, on account of the different anatomical disposition of the

lymphatic system in the female, comparatively rare; nevertheless, Galloway (1926) recorded his familiarity with typical inguinal buboes in Chinese and Japanese prostitutes in Singapore. Most of the cases of inguinal buboes in women who have given a positive intradermal test (see below) have been reported among prostitutes by French writers, though definite evidence of the infection of wife by husband has been obtained in an English case under the Editor's care.

Esthiomène and stricture of the rectum.—Esthiomène is an ulceration of the vulva associated with elephantiasis of the labia, formerly thought to be tuberculous. Stannus and others now believe that esthiomène is the counterpart of lymphogranuloma inguinale in the male. It has been recorded in all the countries of Europe and America, but there are very few references to it among tropical races, though Chesterman on the Congo found typical cases amongst the native women, and also saw the genito-ano-rectal syndrome there. Gray and Yieh, from Shanghai, described four cases in Chinese females. The primary lesion is probably hidden in the posterior wall of the vagina, and the ano-rectal lymphatic gland is the first to be attacked. The infiltration of this gland extends, via the lymph-flow, to the anterior part of the vulva, and posteriorly to the rectum, resulting in the genito-ano-rectal syndrome, and finally scarring of the glands leads to rectal stricture.

Fibrous stricture of the rectum, in both sexes, is probably due to the same virus. Authorities are now agreed that syphilis cannot be held responsible. Rectal stricture appears to be more frequent in Europeans than in native races, though Maxwell reported it comparatively frequently in China; Gray recorded it in both sexes in Nigeria, and Chesterman on the Congo. Rajam, in Madras, in a clinical study of lymphogranuloma and allied conditions, reviewed 183 cases of poradenitis, and found buboes in 99 males and 2 females, and the genito-anal syndrome in 18 males and 8 females. The virus spreads from the initial site of implantation by the lymphatics to the inguinal and pelvic glands, and later in the female the lymphatics of the anus and rectum become involved, producing at first proctitis and, later still, stricture of the rectum. In the male stricture of the rectum follows the occurrence of a primary lesion in the rectum. The following varieties are recognized:—

- (1) Anal stricture in women associated with esthiomène.
- (2) Annular rectal stricture.
- (3) Tubular rectal stricture.
- (4) Rectal communicating strictures from ulceration between the rectum, bladder, vagina, prostate and seminal vesicles.

In 1932 Frei reported that 80 per cent. of cases of the genito-ano-rectal syndrome gave a positive intradermal test.

Extra-genital infections.—Extra-genital infections have been recorded on the tongue, followed by glandular enlargements in the neck, by Curth; in the axilla by Hellerström; and on the foot by Lépinay and Grévin. A possible relationship with regional ileitis (Crohn's disease) was suggested by Likely and Lisa; they recorded a case in which multiple

granulomata of the ileum were present with frank lymphogranuloma of vulva, vagina and rectum.

A few cases of meningo-encephalitis due to the virus of lymphogranuloma venereum have now been recorded.

Ocular lymphogranuloma.—This was described by Macnie (1941). The whole globe may be covered with granulation tissue and the washings of the conjunctival sac will infect monkeys. Curth and Sanders found that a number of cases of uveitis and kerato-conjunctivitis simulating Parinaud's conjunctivitis gave positive intradermal tests; sometimes there is conjunctivitis with ciliary congestion. Fundus changes have been reported, also peripapillary ædema, dilatation and tortuosity of the veins.

Complications.—Sometimes, if too much lymphatic tissue is removed by excision of the glands, an elephantoid condition of the leg and scrotum on



Fig. 109.—Climatic bubo two months after incision and circumcision, showing sinus formation.

(H. Wolfe Cowen.)

the affected side may develop (Fig. 109). This is a grave objection to surgical interference, added to the fact that secondary sepsis is very likely to ensue. Rupture of extensive lymphogranulomatous suppuration into the bladder has been recorded.

Diagnosis.—The diagnosis of climatic bubo and lymphogranuloma inguinale has been placed upon a scientific basis by the introduction of the intracuti-reaction (intradermal test) of Frei (1925), which is now known as the Frei-Hoffmann reaction. The antigen was originally prepared from the inflamed gland tissue.

Frei's original method of preparing antigen for the skin test consisted of withdrawing the pus from a gland which has undergone softening, but not fistulation. The aspirated pus is mixed with physiological saline, in the proportion of one part to five parts in a sterile tube, and immediately put up in 0.5 ml. to 1 ml. doses in Jena hard glass ampoules. Thus prepared, it is heated to 60° C. for two hours over a water bath, and the following day at 60° C. for one hour. The antigen should be preserved at a low temperature unexposed to light. Antigen

can also be prepared from mouse brain or from the yolk sac of the developing chick embryo. Tests must be repeated every three months, and should give negative reactions in skin of normal and control patients suffering from *ulcus molle*. Careful experiments at the Albert Dock Hospital, London, with a controlled antigen prepared as above, have been satisfactory.

Ottolina (1941) claimed that intradermal injection of 0·3 ml. of cerebrospinal fluid from a previously proven case of lymphogranuloma gives a positive reaction. The cerebrospinal fluid is concentrated *in vacuo* from 10 ml. to 2 ml. before

injection.

The Frei Hoffmann test.—The test is carried out on the same lines as the Dick or Schick sensitization tests: 0·1 ml. of antigen is administered intracutaneously in the forearm, causing a wheal 8–10 mm. in diameter. Physiological saline or Dmelcos chancroid antigen is administered on the other forearm as control. A positive result usually appears at the end of 24–48 hours and may vary in size from a circle of 1½ in. in diameter to a considerable reaction about 3 in. in diameter. German writers have noted a hard mass ("Ein harter Knochen") of infiltrated skin which may persist for a few days. This never occurs in negative cases.

In biopsy specimens the essential lesion consists of little pin-point epithelioid formations scattered throughout the lymphatic gland and giant cells are commonly seen. A greater proportion of cases can be diagnosed by this method than by the intradermal tests.

The Wassén test consists of producing a fatal encephalitis in mice by inoculation

of the virus.

It should be noted that a positive intradermal test may be obtained in trachoma, ornithosis and psittacosis and virus pneumonitis.

The disease must be differentiated from soft sore, filarial adenitis, and plague, especially the ambulant form. In China, especially, lymphogranuloma buboes have to be distinguished from pestis minor; they have also to be differentiated from femoral hernia, but these two conditions may be associated. Tularæmia may also have to be differentiated.

Blood changes.—There is usually a leucocytosis accompanying the suppuration. In the Editor's cases this has invariably been so; the leucocyte counts vary from 8,000 to 27,000, but no cell-type is particularly affected.

Serological changes.—Hyperglobulinæmia is constantly present. The total proteins are between 8·1 and 10·3 per cent. in florid cases. The serum albumin is about 3·9 per cent.; serum globulin 3·9 to 5·6 per cent.

Combes (1945) found that 90.5 per cent. of his cases gave a positive formol-gel test and that there was a decided tendency to return to normal after a clinical cure. Therefore hyperglobulinæmia is of value in determin-

ing the activity of the disease.

A complement-fixation test has been described by McKee and his colleagues. The antigen, lygranum (M.L.), stored at freezing point, is made from infected lungs of mice ground up to make a 10 per cent. suspension. The readings are taken at the end of thirty minutes at 37° C. The lowest initial dilution of serum is 1 in 2.

Here again other viruses of the lymphogranuloma venereum-psittacosis group may give a positive complement-fixation test. Tests with virucidal antibodies show, however, that the members of this group of viruses are not antigenically identical.

Treatment.—In the lymphogranulomatous stage the inflamed gland, if discrete, can be excised, and the spread of further mischief appears to be avoided, but surgical interference to lay open the suppurating sinus or remove large masses of lymphatic tissue should be strongly deprecated for, as a result, the gland tissue may become secondarily infected with pyogenic organisms, a permanent lymphatic sinus may form, or chronic lymphatic obstruction may ensue. Usually, excision of the mass when suppuration is present is not followed by clean and rapid healing, but by the formation of sinuses (Fig. 109). Stammers and Law found that surgical removal of the originally infected "feeding gland" may lead to the subsidence of a larger group of secondarily involved glands.

During the acute stage of the disease, treatment should consist of rest and

the application of soothing dressings.

Protein-shock therapy is often followed by dramatic results, and the Editor has had considerable experience of this method of treatment. It is especially advantageous when suppuration has commenced, and should be combined with aseptic aspiration of the gland. This aspiration may have to

be repeated several times.

Typhoid-paratyphoid vaccine (T.A.B.), or "Pyrifer" is employed, commencing with 50 million given intravenously and gradually increasing to 200 or 300 million, injections being given every third day. Two or three reactions are usually required before the buboes dry up and the surrounding induration disappears. This treatment should be combined with rest in bed, and antiphlogistine dressings. When there is active suppuration it is advisable to aspirate, making a small opening with a tenotomy knife, packing with gauze, and using silkworm stitch as a seton.

Vaccine therapy.—The vaccine is prepared by excising a convenient portion of the gland mass, which is cut up into small pieces, dehydrated over calcium chloride, emulsified in saline and injected in increasing doses every second day, but no reliable results have so far been obtained by this method.

Treatment by drugs.—Sulphonamides.—MacCallum and Findlay, by means of chemotherapeutic experiments on the virus of lymphogranuloma in the mouse, have shown that sulphonamides have a definite value. At present it is impossible to say why viruses of the lymphogranuloma venereum-psittacosis group are alone susceptible to sulphonamide action, while so many other viruses are insusceptible, but the evidence so far obtained seems to point to the fact that living virus may still be obtained from the brains of certain mice after prolonged treatment with sulphonamides.

In the treatment of the disease in man Montel (1937) in Indo-China found the French preparation, rubiazol, curative, if given in courses over a prolonged period. Earle (1939) reported on the value of sulphapyridine, but recent reports indicate that in actual practice the results are disappointing.

The best two drugs are sulphathiazole and sulphadiazine. In early cases 6 grm. should be given on the first day of treatment, followed by 3 grm. daily for 20 days (a total of 66 grm.). Sulphonamides have also given remarkable results in cases of conjunctivitis due to lymphogranuloma venereum virus.

Aureomycin.—Greenblatt (1950) states that lymphogranuloma does not respond to penicillin or streptomycin, but that aureomycin appears to be more effective in

 $^{^{1}}$ Pyrifer is a Bact. coli preparation in strengths from 50–500 million, prepared by Aristopharm Ltd. Switzerland.

the later, rather than the earlier, stages. Sinuses, proctitis, and inflammatory strictures show marked improvement when 70--100 grm. are given over 37--60 days, but ulcers show poor response. Chloromycetin is not nearly so good. Alergant (1950) gives 250 mgm. per mouth every six hours to a total of 7 grm. Robinson and colleagues (1950) gave intramuscular injections in amounts from 0.56--3.6 grm., but these were too painful. Proctitis shows great improvement. The complement fixation test is unsatisfactory as an index of therapeutic effect.

Treatment of rectal stricture.—The treatment of rectal stricture is difficult. Palliative measures consist in dilating by graduated bougies and injecting antiseptic solutions to cure the ulceration. Operative measures depend entirely upon the type of stricture present; Lockhart-Mummery gives the following alternatives: internal proctotomy; complete proctotomy; excision of the stricture or of the rectum; and colostomy. Bensaude and Lambling, on the other hand, consider diathermic dilatation to be the best method, applied for twenty minutes every two or three days, for ten to twelve applications. Oil-soluble local anæsthetics, such as proctocaine, are best for post-operative rectal pain.

The medical treatment of rectal stricture and esthiomène has been improved by the introduction of sulphonamides. Shropshear claimed success with sulphapyridine, in doses of 2 grm. daily, for fifteen days, with a seven- to ten-day interval, after which the course is repeated. Two patients required 108 grm. in two fifteen-day treatments before symptoms disappeared. In women sulphapyridine checks leucorrhæa and heals the ulcers. Sulphadiazine, if continued over long periods of six months to a year, has given remarkable results. One method is to give the sulphonamide for 10-12 days every month. Aureomycin should be of value.

CHAPTER XLI

ULCERATING GRANULOMA OF THE PUDENDA

Synonyms.—Granuloma Venereum, Granuloma Inguinale.

Definition.—An infective and granulomatous condition of the pudenda, widespread in some parts of the tropics, conveyed by sexual contact and auto-inoculation.

Geographical distribution.—Ulcerating granuloma is widely diffused in India, Guiana, Brazil, West Indies, Porto Rico, Papua, Pacific islands, and Northern Australia; sporadically it occurs in the Southern United States, on the West Coast of Africa, and in Southern China. De Vogel relates that in the southern region of Dutch New Guinea this disease appears in epidemic form and threatens the extinction of the local tribes. In only one case has spontaneous cure been observed. A few cases have been found outside the tropics. One is described from Scotland by Fergusson and Roberts (1953).

Ætiology.—There is good reason for believing that the disease is generally, though not invariably, venereal; very rarely, extragenital lesions have been observed. Cleland and Strangman in Australia, Flu in Surinam, and Aragão in Brazil described certain parasitic bodies within the large mononuclear cells from scrapings of the lesions. The organism is like a short bacillus with rounded ends, and measures l μ by 0·2 μ ; it was described and named Calymmatobacterium granulomatis by Donovan, and later by Araujo. It is now known as a bacterium, allied to B. mucosus capsulatus. It is termed in U.S.A. Donovania granulomatis and can be grown at 37° C. in the yolk sac of chick embryo only (Dunham and others). The secondary invader may be the non-hæmolytic anaërobic streptococcus described by Meleney (p. 658).

Dienst and Greenblatt (1943) have not confirmed previous observations, and now think that the Donovan bodies are protozoa, in no way related to bacteria (the diphtheria group) and have confirmed its true ætiology by reproducing the disease in negro volunteers (1939). The organism is selective for its particular host, reproduces by multiple segmentation within endothelial cells and is affected by antimony. The bodies are further distinguished by retaining basic fuchsin stain, when exposed to weak decolourizing agents. The smear from an ulcer is fixed, flooded with 0.5 per cent. aqueous fuchsin for two minutes, then washed with water and 0.5 per cent. citric acid until the dye ceases to leave the smear (5 sec.). The film is then washed in water and counterstained with 1 per cent. aqueous aniline blue for 5 minutes. Donovan bodies, when stained by hæmatoxylin and silver salts, have a closed "safety pin" appearance because of the ovoid shape and dense bipolar staining. A positive intradermal reaction with triturated infected yolk sac as antigen containing Donovan bodies has been demonstrated by Dienst (1947).

Age and sex.—Ulcerating granuloma has not been recorded before puberty; it has been found only after the age of 13 or 14, and up to 40 or 50. It occurs in both sexes, but more often in women, especially where polyandry is practised. Transmission by *Phthirus pubis* is suggested by Butts and Olansky (1946).

Pathology.—Histologically this disease is allied to rhinoscleroma, and the close association between these two diseases in Sumatra has been emphasized by Snijders. It is a reticulo-endotheliosis and on microscopical examination the new growth at the margins of the sores is found to be made up of nodules, or

masses of nodules, consisting of round cells having large and, usually, badly-staining nuclei. These cell-nests of Malpighian cells are embedded in a delicate fibrous reticulum. The predominating cells are the plasma and endothelial cells forming small polymorphonuclear micro-abscesses described by Allen (1948). An important feature in the histopathology is a peculiar pathognomonic cell described by Pund and Greenblatt (Fig. 110). It is a large mononuclear varying from 25 to 90 μ in diameter, probably derived from a plasma cell. The specific cell, laden with the so-called Donovan bodies, can be shown best by the Dieterle silver impregnation method in which these bodies appear as dark brown or black elongated ovoid masses with intense bipolar staining. The nodular masses are, for the most part, covered by epithelium, their under-surfaces



Fig. 110.—Ulcerating granuloma of pudenda showing the pathognomonic cell and contained Donovan bodies. (After Pund and Greenblatt, "Archives of Pathology.")

merging gradually into a thick, dense, fibrous stroma in which small clusters of similar round cells are here and there embedded. The growths, though very vascular, contain no hæmorrhages; and there are no signs of suppuration or of caseation, no giant cells, and no tubercle bacilli. In vertical section of the small nodules the round-cell mass will be found to be wedge-shaped, the base of the wedge being towards the surface; the deep-lying apex is usually pierced by a hair or two. The growth is found around sebaceous follicles, blood-vessels, lymphatics, and sudoriferous glands; but it is especially abundant, and most deeply situated, around hair follicles.

Symptoms.—The incubation period appears to be comparatively short, from two to eight days after sexual contact, but it may be as long as twelve weeks. The disease commences in the great majority of cases somewhere

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on the genitals, usually on the penis or labia minora, the pubes, or groin, as an insignificant, circumscribed, nodular thickening and elevation of the skin.

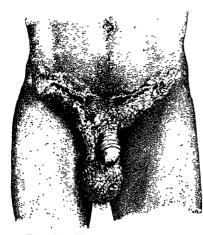


Fig. 111.—Ulcerating granuloma of pudenda in male.

The affected area, which on the whole is elevated above the surrounding healthy skin, and covered with a very delicate, pinkish, easily-rubbed-off epithelium, excoriates readily, exposing a surface which tends to bleed and break down, although rarely ulcerating deeply. The disease advances in two ways: by continuous eccentric peripheral extension. and by auto-infection of an opposing surface. It exhibits a distinct predilection for warm and moist surfaces. particularly the folds between the scrotum and thighs, the labia, and the flexures of the thighs (Fig. 111). Its extension is very slow, years elapsing before it covers a large area. Concurrently with peripheral extension, a dense, contracting, uneven.

readily breaking down scar forms on the surface travelled over by the coarsely or finely nodulated elevated new growth which constitutes the peripheral part of the diseased area. Occasionally, islands of active disease spring up in this scar tissue; but it is at the margin of the implicated



Fig. 112.—Ukerating granuloma of pudenda in female. Australian aborigine. (Dr. H. Basedow, Adelaide.)

patch that the special features of the affection are best observed. In cases of long standing the partially-healed areas are covered with thin

depigmented skin and thus show up as white patches.

In the female (Fig. 112) the disease primarily attacks the crura of the clitoris, thence extending into the vagina, over the labia, and along the flexures of the thighs. The women thus affected are rendered sterile. In the male the disease may spread over the penis, involve the glans, scrotum, and upper part of the thighs (Fig. 113). Occasionally, the glans penis is not involved. In either sex it may spread in the course of years to the pubes, over the perineum, and into the rectum, the recto-vaginal septum in the female ultimately breaking down. At times, a profuse watery discharge exudes, and even drips from the surface of the new growth, soiling the clothes, soddening the skin, and emitting a peculiarly offensive odour. In

this condition the disease, slowly extending, continues for years, giving rise to inconvenience, and perhaps seriously implicating the urethra, vagina, or anus, but not otherwise materially impairing the health. In neither sex do the lymphatic glands become affected. The disease continues entirely local, but in the process of cicatrization the lymphchannels may become blocked, and pseudo-elephantiasis of the genitalia may occur. Impassable strictures of the urethra may result, and recto-vaginal fistulæ are common. It may even cause death by eating its way into the bladder, causing septic cystitis, as in a longstanding case under the Editor's care.

Diagnosis.—Malignant and syphilitic ulcerations of the groin are common enough; the disease under notice, however, differs widely from these — clinically, histologically, and therapeutically. It is characterized by extreme chronicity—ten or more years; by absence of cachexia or of any tendency to cause death; by non-implication of the lymphatic system as a whole, and by non-amenability to mercury and iodide of potassium.

The disease which it most resembles is lupus vulgaris. From this it differs inasmuch as it is practically confined to



Fig. 113.—Ulcerating granuloma of face and penis in a Chinaman. (Dr. B. Hawes.)

the pudendal region; tends to follow in its extension the folds of the skin; and is not associated with the tubercle bacillus, giant cells, cascation, or other evidences of tuberculous disease. Unless complicated by a coincident syphilitic infection, the Wassermann reaction is negative. The inefficiency of antisyphilitic treatment soon convinces the physician that the ulceration is not due to this disease. Its characteristic mode of spread suffices to distinguish it from epithelioma and carcinoma. The discharges from ulcerating granuloma have,

moreover, a peculiar acrid smell. Pund and Greenblatt described a fungating form affecting the cervix uteri in negresses, which greatly resembles the ulcerative and vegetative type of carcinoma of the cervix. It has also to be distinguished from gonorrhœal endocervicitis and from simple erosions. The characteristic cells (plasma cells, etc.) may be demonstrated by biopsy.

Treatment.—Scraping and caustics, including the actual cautery, have been freely employed; but, although some improvement may be effected, new nodules almost invariably spring up in the resulting cicatrix. Complete excision, where practicable, offers the best chance of permanent cure; such a proceeding has to be undertaken before large areas and important passages have become involved.

Treatment by intravenous injections of tartar emetic, introduced by Aragão and Vianna in 1913, has proved successful, although in a small proportion of cases relapses occur. The drug should be injected on alternate days, commencing with 1 gr. dissolved in distilled water and gradually increasing by the same amount up to the maximum individual dose of 2 gr., but the total amount required to effect cure varies within wide limits. The Editor had one with a suprapubic lesion which healed completely after a total of 17½ gr., while others required 170 gr. or more. Cicatrization usually takes place rapidly, but indolent ulceration may persist. Stibacetin, neostibosan, and other pentavalent compounds of antimony are more efficacious than tartar emetic, in total dosage of from 3 to 4 grm. Giglioli, in British Guiana, gave two courses of seven intravenous injections with 45 days between each course. Each consisted of 0.1-0.6 grm. of stibacetin dissolved in 20 ml. of normal saline, and this drug was successful in cases resistant to tartar emetic. Anthiomaline, as in lymphogranuloma, has also been used with success. On the other hand Earle considers found (a trivalent antimony salt) efficacious (see p. 715). The Editor has found it advisable to dress the open granulations daily with an ointment containing 1 per cent. of antimony tartrate in white vaseline. It should be left on for two hours, then wiped off carefully, and the sore washed with boracic solution and dressed with boracic ointment. Radiant heat applied to the ulceration has proved beneficial, while touching indolent spots with a silver-nitrate stick will sometimes promote healing. Tartar-emetic treatment may be combined with X-ray and with protein-shock treatment (Hanschell). These should alternate with tartar emetic injections. Operative measures, such as the amputation of a badly ulcerated glans penis, may become necessary.

In addition to medicinal means, it is often necessary to open up sinuses

and to cauterize undermined margins by the electric cautery.

Many observers have drawn attention to types of ulcerating granuloma which are unaffected by antimony. Meleney drew attention to the curative action of zinc peroxide in the treatment of anaërobic organisms in acute surgical infections. The standard preparation is one which, when sterilized and suspended in distilled water, consistently yields oxygen while itself remaining soft. It must be rubbed into the wound, especially at its spreading margins, in gangrenous infections of the skin due to synergistic

¹ To make antimony-tartrate outment, the necessary amount of antimony tartrate is first dissolved in a small quantity of liquid parafin and then made up to strength with white Vaseline. The ointment must not be spread on the healthy skin.

bacterial action, and in undermining burrowing ulcers of the non-

gangrenous type. (Fig. 114).

The liberation of oxygen depends upon the presence of water, and therefore zinc peroxide cannot be employed in oily solutions. The best preparation is that of the Du Pont Chemical Co., Niagara Falls. It should be sterilized at 140° C. for four minutes; 5–25 grm. are put in large test-tubes, the contents of which are mixed by means of a syringe with enough distilled water to give a homogeneous suspension with the consistency of 40 per cent. cream. It is then spread so as to come into contact with every part of the infected surface, particular care being taken to see that it penetrates the undermined skin and into the sinuses, for which purpose it is frequently necessary to use a short catheter. Strips of gauze or silk are dipped into the suspension, and introduced into the sinuses, but the dressings should



Fig. 114.—Ulcerating granuloma of the pudenda infected with non-hæmolytic streptococcus. (Dr. Butterfield.)

To show healing with zinc peroxide treatment and extensive scar-tissue formation.

be changed daily (Fig. 114). It may be found advantageous to syringe out the sinuses with hydrogen peroxide.

Sulphonamides, especially sulphapyridine, have been successfully employed. Ross and others recorded success with 3 grm. daily for fourteen days in early lesions. Earle regarded sulphonamides as useful adjuvants to antimony treatment.

Penicillin.—Turner (1945) has treated seven cases with penicillin which had proved resistant to antimony. It was given by intramuscular injection up to 4,000,000 units. The injections were given at intervals of

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3-4 hours followed by local application of penicillin cream. Clinically all showed constitutional improvement. It was concluded that penicillin had no direct action upon the original disease, but cleared up secondary infections and thereby paved the way for further antimony treatment.

Streptomycin.—Greenblatt (1947) considers the success with this treatment remarkable. Fifty-eight patients were treated with 3·3–9·4 grm. of streptomycin, given intramuscularly in divided doses, four-hourly, to a total of 0·3–4 grm. per day. A course of 4 grm. daily for five days proved most adequate. Although lesions are still present, progressive healing still takes place and complete healing is noted within one to three weeks. The results are far superior to those obtained with antimony. Toxic effects noted were cylinduria without renal involvement and some vestibular dysfunction. Recent experiences tend to show that dihydrostreptomycin is less toxic and equally effective.

Other antibiotics.—Robinson (1950) has stated that aureomycin, chloromycetin and streptomycin are all effective, but that the last-named remains the drug of choice. Greenblatt and others (1949) have reported especially good results with aureomycin by the mouth in 46 patients, some of whom had been resistant to streptomycin. The average dose was 20–30 grm. in 10–15 days. The smallest dosage was 10 grm.: the largest 70 grm.

Prophylaxis.—As this disease is most certainly spread by sexual connection, prevention consists in the avoidance of illicit intercourse, especially with native women.

occur after the fifth year and attain their maximum incidence during the third decade. In a mixed community this incidence is highest in Indians. The majority occur during periods of low rainfall and low relative humidity.

Ætiology.—Prowazek attributed these ulcers to Spirochæta schaudinni, and these spirochætes are present, together with fusiform bacilli, in most ulcers.

Although sloughing phagedæna is evidently a germ disease, it is not readily communicated by ordinary inoculation either to man or to the lower animals. Apparently a concurrence of certain unknown conditions is essential. Lloyd Patterson, however, succeeded in producing a characteristic sore by bandaging a swab smeared with discharge from a typical sore on to the surface of an abrasion, from which the scab had been removed, and this has recently been confirmed by Hare (1948).

Sloughing phagedæna is apt to attack the half-starved, malaria-stricken pioneers in jungle lands, over-driven labour gangs, and soldiers campaigning in the tropics. In such circumstances a slight wound, an abrasion, even an insect-bite, or an old chronic ulcer may serve as the starting-point for one of these terrible sores. Where yaws and sloughing phagedæna are co-endemic, the sores of the former may become infected with the virus of the latter, and serious sloughing and cicatricial contractions result. The feet and legs, being most exposed to injury, are the most frequent locations of this form of ulceration; but the arms, or any other part of the body, may also be attacked. The blood-calcium content, blood-sugar and blood-urea are said to be much diminished, probably as the result of deficient dietary (McCulloch). On the other hand, the Editor has observed several severe cases in otherwise healthy and well-fed Europeans in whom a dietetic deficiency could hardly be seriously considered.

Clements in Melanesia and James in the Solomon Islands were strongly of the opinion that diet deficiencies (especially B₂), debility and climatic factors combine in predisposing to ulcus tropicum. For instance, the incidence in sago-eaters is vastly greater than in those who subsist on taro. Tropical ulcer is rarer in West African native troops, whose diet includes a ration of red palm oil, than in East African soldiers, who do not receive this. A close relationship with chronic malaria appears to be possible in the epidemic form of this disease, and stress is laid upon the importance of Buxton's line of separation between the malarial and non-malarial Pacific Islands, which also marks the separation between phagedenic and ulcer-free islands. It is apparently true that the virulence of the organisms responsible for ulcus tropicum is increased by transmission amongst susceptible people. Marsh and Wilson in Persia describe it as the result of filth, food and friction.

Symptoms.—If the disease occurs in previously sound skin, the first indication is the formation of a larger or smaller bleb with sero-sanguinolent contents. The bleb may be attended with some pain and constitutional disturbance. When, in the course of a few hours, the bulla ruptures, an ash-grey, moist slough is exposed. The sloughing process rapidly extends in all directions until the skin and subcutaneous fascia over an area of one to many inches in diameter are converted into a yellowish, moist, horribly stinking slough. After a few days the centre of the slough begins to liquefy, the sore still continuing to extend at the periphery. In the course of a week or longer the sloughing process may cease and the slough be gradually thrown off (Fig. 116). Then it is seen that not only have the skin and superficial fascia been destroyed, but in bad cases possibly muscles, tendons, nerves, vessels, and even the periosteum of the bones, have shared in the gangrenous process. Fortunately, in many instances, the deeper

structures are spared, the disease being relatively limited and superficial. Sometimes, however, important structures, including joints, bones, and large blood-vessels, are destroyed; in such cases, even if life be spared, great deformity may ensue from different forms of ankylosis, or from strangulation of a distal part by a contracting cicatrix, necessitating amputation (Fig. 117).

Healed tropical ulcers leaving behind tissue-paper-like scars with pigmented edges are easily recognizable, and they constitute the familiar

hall-marks of former prisoners of war in Japanese hands.

Diagnosis has to be made from the ulceration of yaws, syphilis, amæbic ulceration of the skin, oriental sore, varicose ulcers, and veld sore, and is usually not very difficult, a final diagnosis being arrived at by exclusion.

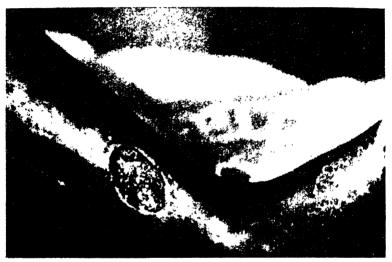


Fig. 116.—Ulcus tropicum.

Treatment.—As recent observations in Kenya Colony and Tanganyika Territory have shown that dietetics play an important part in the production of ulcus tropicum, it is of the first importance to correct any cachectic state. Thus, good food, fresh vegetables, lime-juice and quinine are almost invariably indicated. Corkhill in the Sudan found that much the same conditions hold there; cod-liver oil dressings, for instance, combined with a liberal vitamin A dietary give good results. Opium in full doses, not merely to assuage pain, but on account of its special action on the phagedænic process, is usually of great service.

The most important advance in treatment has been the introduction of penicillin. Numerous papers published during the recent war have testified to this. Findlay, Hill and Macpherson (1944) published a series of 25 cases of long duration in which healing took place after injection of 100,000 units within 24 hours and the application of penicillin ointment (250 units per grm.). Great improvement took place immediately and in

a few days the ulcers had become practically sterile. Hare (1948) found that fusiform bacilli disappear and that the effect is immediate. Complete healing takes place in a month.

O'Brien (1951) has stated that the most satisfactory treatment is occlusion plaster with parenteral penicillin and skin grafting as follows:—

(1) Hypertonic saline dressing, applied hot or cold three times daily.

(2) Antiseptics such as eusol, alone or combined with hydrogen peroxide. All cases are cleared with 1 per cent. solution of C.T.A.B. (Cetyltrimethyl ammonium bromide). Brilliant green 1:500 is used in final stages to prepare the area for grafting.



Fig. 117.—Ulcus tropicum: acute case in a European, eventually causing loss of leg.

(3) Topical application of a powder of crystalline penicillin—10,000 units with sulphathiazole 0.6 grm., plus magnesii carbonas ponduosus to 1 grm., and a cream containing penicillin 500 units per grm.

Preparation for grafting.—Saline dressing is applied and the first course of penicillin started; the surface is dusted with P.S.P. (penicillin, sulphathiazole and mag. carb. pond.) and covered with dry dressing. The limb is encased in a light plaster cast. Six days later the area selected is prepared with C.T.A.B. and a second course of penicillin begun.

Total excision of the ulcer area, followed by Thiersch-grafting. offers the only means of ultimate success. By means of a large curved bistoury (curved on the flat in addition to the normal curve) the whole of the

infected tissue is removed. The ulcer is excised under spinal anæsthesia and not scraped. The resulting wound should be dressed with eusol and ointment twice daily until the surface is clean. Afterwards, a dressing of B.I.P.P. should be applied once daily for some days until it is certain that there is a granulating surface. The site is now treated by skin grafting. According to Enzer, when the Thiersch methods fails, "pinch grafting" of small circular patches of whole skin distributed over the area should be employed. It is said that complete healing takes place in 14 days. The grafts should be dressed with an emollient ointment, e.g., Tulle Gras Lumière (Anglo-French Drug Co., 238, Gray's Inn Road, W.C.1). Workers in Kenya agree that the grafts usually take readily, and the stay in hospital after operation is one of twelve to nineteen days.

Other antibiotics.—Ampofo and Findlay (1951) recommend 3 per cent. aureomycin applied locally as of considerable value. Dressings must be changed daily. Oral administration of the drug increases the rate of healing.

Later (1952) they claim that terramycin ointment is even better. Huttel (1951) in Gabon treated three ulcers by curretage and application of a firm dressing of a mixture of terramycin (5 grm.), and paramidophenyl sulphamide (1162F) sulphamilamide, 100 grm.

VELD SORE

Synonyms.—Septic Sore; Desert Sore; Barcoo Rot.

Geographical distribution.—This peculiar ulceration is widely distributed in the tropics and subtropics wherever desert conditions exist. It has long



Fig. 118.—Culture of Klebs-Löffler bacillus obtained from the veld sore shown in Fig. 117. (Dr. H. K. Giffen, Assiut, Egypt.)

been known in Queensland and the Northern Territory of Australia. It affected the British troops in the Sudan and South African campaigns, and caused a very considerable amount of disability in Gallipoli, Egypt, Palestine and Iraq during the 1914–18 war. It has also been prevalent in British troops in Palestine, Libya, Abyssinia, Eritrea and the Middle East during 1939-1945 war. In South Africa it is familiar to sportsmen and travellers.

Ætiology.—The cause of this condition had long been obscure.¹ In 1916 Craig, in the Sinai Desert, demonstrated the diphtheria bacillus in the lesions. Whether this covers the ætiology of all veld sores cannot at present be affirmed, but that a certain proportion are diphtherial in origin may be taken as established. By sterilizing the surface of the sore with absolute alcohol and scraping the clear surface, a culture

⁹ H. H. Scott (personal communication) isolated the diphtheria bacillus from a veld sore in the S. African war in 1901, and succeeded in curing it by application of antidiphtheritic serum.

of the Klebs-Löffler bacillus was obtained on Löffler's serum. This organism was pathogenic to guinea-pigs and quails, and its lethal effects could be neutralized by injection of antidiphtheritic serum. In the serous contents of the blebs the typical granular bacillus was observed in stained preparations. (Fig. 118.)

The desert sores, as the Editor observed them among British troops, occurred most frequently in men of mounted units, especially those associated with horses and camels, and in the 1939-1945 war similar lesions have also been seen in cavalrymen. The rate of incidence coincides with that of a widespread epidemic of faucial diphtheria. Cameron and Muir (1942) described the lesions as they occurred in mounted units in Palestine. Acute and chronic stages were recognized. Paralyses occurred in a number of patients in whom there was no other focus of infection than the skin. Not all sores on exposed parts are necessarily diphtherial in origin; some are primary staphylococcal. In Eritrea and Abyssinia it was noted by Louw that the men of mechanical units with oil or grease on their clothing suffered less than others from septic ulceration. Excessive dryness of the skin is a predisposing factor.



Fig. 119.—Veld sore on leg containing growth of Klebs-Löffler bacillus. (Dr. H. K. Giffen.)

Symptoms.—The sores occur almost invariably on the exposed parts, mainly those covered by hairs, such as the dorsum of the hand, the fore-arm, the elbows and knee-joints. Sometimes the lesions occur on the face, over the eyebrows and on the cheeks. They may arise de novo, or be superimposed on some abrasion.

A regular sequence of events precedes the actual ulceration. At first a vesicle full of straw-coloured fluid makes its appearance, generally in the vicinity of a hair follicle; it may vary considerably in size. The pain it occasions is quite out of proportion to the size of the lesion. On bursting it leaves behind a shallow ulcer covered with a thin grey pellicle. The raw ulcerated surface is exquisitely tender, and it may continue to spread peripherally. (Figs. 119, 120.)

After the inflammatory changes have lasted two or three weeks the ulcers enter upon a chronic stage. Then they are characteristic in appearance and perhaps are more familiar to practitioners than in the incipient stages. The ulcers are punched-out, circular, with undermined edges and thickened margins; their base is covered with grey-coloured and scaly débris, beneath which can frequently be distinguished an adherent membrane, but little or no pus is discharged. The peculiar ulceration which results is most intractable, and resists all external forms of medication; the edges become indurated, and

the thickened tissue has a cyanotic appearance. In sores in which healing does take place, a thin paper-like scar remains for several years. The actual ulceration

may continue for two years or longer.

The Klebs-Löffler bacillus can be isolated from the primary lesions; from the chronic ulcerations it is recovered with difficulty, being overgrown with staphylococci and other organisms of suppuration. The best medium is Marshall's tellurite.

Diphtheritic pareses, or paralyses, have been observed in association with these sores; in one series this complication occurred in 27 per cent. Paralysis of the palate, arms and legs, and accommodation paralysis of the iris have been recorded. There may be ataxia, loss of knee-jerks, anæsthesia and incoordination, recalling at first sight locomotor ataxia or beriberi. Walshe pointed out that the initial local paresis is in anatomical relation to the site of the infective



Fig. 120.—Veld sore. Primary lesion on adductor aspect of thigh; secondary contact sore on scrotum. (Capt. Manton.)

focus, and may be taken to indicate direct passage of toxins from the diphtheritic lesion along the neural channels to the central nervous system. Accommodation pareses, on the other hand, usually appear in the second week, no matter what the site of the local lesion may have been. Polyneuritis is usually delayed for three weeks or longer.

Ward and Mason (1945) have described similar cases during the Burma campaign. The first symptom of nervous involvement was blurring of vision, tingling, numbness and coldness of extremities. On examination there was asteriognosis and ataxia.

Treatment.—The specific treatment for this kind of ulceration is antidiphtheritic serum, which has a very striking effect in healing up ulcers that have persisted for a year or even longer. At least 20,000 units should be given, and should be injected subcutaneously or intramuscularly in the vicinity of the sores. Sulphonamides by the mouth have been found useless, but in chronic cases staphylococcal vaccines are advocated, together with compresses of hypertonic saline, cod-liver oil dressings, and elastoplast bandages. In some cases silver nitrate stick is beneficial. Saline solutions of penicillin applied to sores accelerate healing.

In staphylococcal sores sulphonamide paste and acriflavine ointment bave been employed (acriflavine, 0·1 per cent.; adeps lanæ anhydrous 45 per cent.; water 100 per cent., to which is added 10 per cent. sodi sulph. for osmotic effect). Penicillin in full doses should be used.

Prophylaxis.—Protection of exposed parts of the body, especially the knees, against abrasion in desert regions where these sores occur, is obviously indicated. Mounted men should wear knee-breeches and should not be permitted to ride in shorts. The application of antiseptic lotions to any abraded surface at the earliest possible moment is also indicated. As there is some evidence that dried horse-manure may act as a nidus of the bacillus, care should be taken to avoid contact with this as far as possible.

PEMPHIGUS CONTAGIOSUS (PYOSIS MANSONI); WILD FIRE

Geographical distribution.—Pemphigus contagiosus is very common in South China during the hot weather; in some years it may even be described as epidemic. It is perennial in the Straits Settlements, and it is known in Ceylon, Madras, in North Queensland, Japan, and America. European are more liable to it than native children; European adults are by no means exempt, but the native adult is rarely affected.

Ætiology and pathology.—Like impetigo contagiosa, this is undoubtedly a germ disease, caused by streptococci and staphylococci. Manson originally found a diplococcus in the epidermis and in the fluid of the blister. Mourão has stressed the 1ôle of β . hæmolytic streptococci of Lancefield's group A.

Symptoms.—Pemphigus contagiosus closely resembles certain forms of the impetigo contagiosa of temperate countries, and is probably a variety. The individual lesions, as can readily be ascertained by inoculation experiments, begin as minute erythematous specks, which rapidly proceed to the formation of vesicles, bullæ, or even large pemphigus-like blisters.

Pemphigus contagiosus may occur in almost any part of the body. In young children it is usually diffuse; in adults it is mostly confined to the axillæ and crutch.

Diagnosis.—Absence of constitutional symptoms, or of a history of such, distinguishes pemphigus contagiosus from chickenpox. Absence of trichophyton elements, and of a well-defined, slightly raised, festooned and itching margin, together with the presence of large blebs and scaling of the epidermis, distinguishes it from ordinary forms of body ringworm—a disease with which, when occurring in the armpits and crutch in adults, it is frequently confounded.

Treatment.—Cleanliness, the frequent use of a corrosive sublimate lotion (1 in 1,000) and a dusting-powder of equal parts of boric acid, starch, and zinc oxide, or ammoniated mercury ointment are specially effective. As the streptococci are penicillin-sensitive this should be injected into every case in total dosage of one mega unit. Sulphonamide compounds, especially sulphapyridine in full doses of 3 grm. daily to an adult, were found effective by Earle. In the school and nursery those responsible for the care of children must be informed of the contagiousness of this unpleasant affection, and measures must be instituted accordingly.

SEBORRHŒA (O'DONOVAN AND MICHAELSON, 1946)

Lesions of the face or scalp, especially those of seborrheic nature, are associated in some with kerato-conjunctivitis which appears to be identical with that described as epidemic virus kerato-conjunctivitis, and is allied to herpes simplex. It is associated also with seborrheic dermatitis. The onset of the skin lesion precedes that of the ocular by a definite short interval of time.

CRAW-CRAW AND ULCERATIVE DERMATITIS

Synonym.—Nodular Dermatitis.

Symptoms.—The term craw-craw is very loosely applied. Emily described under this name a papulo-pustular skin affection which is common in certain parts of tropical Africa and is often the cause of much suffering to the traveller.

Diagnosis.—The hard, horny papules of craw-craw have to be differentiated from scabies, which is common in African natives. They have also to be distinguished from the lichenoid eruptions caused by microfilaria volvulus (p. 778).

Treatment.—Emily described a very efficient treatment. Pustules are opened, crusts removed, and ulcers scraped. Boric-acid powder is then dusted freely on the parts after a thorough scrubbing with sublimate lotion (1 in 1000); borated vaseline is applied on lint, and this is covered by absorbent cotton and a bandage. The dressings are not disturbed for a week, when the parts will be found soundly healed. Similar auto-infective diseases, so common in the tropics, may be treated by prolonged soaking in a warm carbolic-acid lotion (1 in 20), followed by dry dressing with boric powder. Infected slippers, shoes, and stockings should be destroyed. Most cases of so-called craw-craw are in fact scabies.

III. PARASITIC DERMATITIS

CERCARIAL DERMATITIS (SCHISTOSOME DERMATITIS)

Cort in Michigan (U.S.A.) in 1928 drew attention to a special kind of dermatitis produced by Cercaria elvæ, and C. douthitti was soon afterwards found to cause similar lesions. In England and Wales dermatitis after bathing in ponds and reservoirs has been noted by Matheson, Taylor and Baylis as due to C. occilata, a form closely allied to C. elvæ. The cercariæ burrow in the skin, where their heads become arrested and cause a pustular eruption. All these cercariæ are derived from different species of snails, especially Lymnua stagnatilis. C. elva and C. ocellata are large cercarize nearly 1 mm. in length overall, twice that of the schistosome cercariæ; the tail is bifurcated and all possess two suckers. Cercarial dermatitis is commonly known as "sedge-pool itch" or "swimmers' itch," and takes the form of an itching maculo-urticarial dermatitis, later becoming papular or pustular; it may be, after a few days, actually exanthematous. It is always connected with paddling or swimming in infected waters a few days previously. A somewhat similar dermatitis is noted in association with cercarial penetration in Schistosoma hamatobium and S. mansoni infections.

"Sawah itch" in Malaya is caused by cercariæ of a cattle schistosome (Buckley). Paddy itch or "Koganbyo" is a lakeside disease in valleys adjacent to Lake Shingi, Japan, caused by cercariæ of Gigantobilharzia sturniæ. The intermediate host is a snail, Polypylis hæmisphærula. The definitive hosts are starlings, sparrows and wagtails (Hunter and colleagues, 1951). Hunter has found two species of Trichobilharzia responsible for swimmers itch in Seattle. The cercariæ can penetrate the skin of bathers.

CATERPILLAR DERMATITIS

The hairs of various species of hirsute caterpillar may give rise to urticaria and dermatitis in susceptible individuals. Berkowitz (1946) has described attacks of urticaria in troops in New Guinea which reached epidemic proportions. Similar outbreaks have been recorded in Northern Australia. The species is Ochrogaster contraria. In experiments with volunteers some developed local urticaria within a few minutes and this was replaced after 3-4 hours by a pruritic papular eruption.

Earle has described "Fuetazo dermatitis" in workmen engaged in oil exploration on the coast of Equador. This is a blackish-green beetle (Pæderus ornaticornis) 1 cm. in length. A variety of lesions are caused by contact of excretion of this insect, most commonly it is a papulo-vesicular rash. Linear grouping is usually seen on exposed parts, especially on the face. Conjunctivitis also is common. The parts should be washed immediately with soap and water. "Fuetazo" is Spanish for whiplash.

IV. ALLERGIC AND TOXIC DERMATITIS PYRETHRUM DERMATITIS

Pyrethrum dermatitis has been noted in Kenya, and is caused by the leaves and flowers of *Chrysanthenum cinerariæfolium*, which grows at altitudes of 500–7,000 feet and flowers throughout the year. The pyrethrum content is 1–2 per cent. Absorption is facilitated by constant sweating, and exposure to sunlight greatly exacerbates the lesions. Some persons on contact exhibit merely a local dermatitis; others show a widespread allergy. Itching commences at the corner of the eyes, and is followed by lacrymation, an irritating vesicular rash, peeling of the skin, and formation of painful fissures.

Poison Ivy Dermatitis (Dermatitis Venenata)

Many tropical plants cause dermatitis which may assume an erythematous, vesicular or urticarial form. Intimate contact with the plants or its leaves is necessary. Poison ivy (Rhus toxicodendron), poison sumac (R. vernix), poison wood (Metopium toxiferum) in North Eastern and Southern United States cause intense dermatitis. Repeated attacks do not produce immunity. The venom is toxicodendrol. Treatment consists of washing the skin with soap and water; alcoholic or oily solutions must be avoided. Clothes must be decontaminated by immersion in 1 per cent. calcium hypochlorite for twenty minutes.

OTHER FORMS OF DERMATITIS

Several other plants and flowers may cause severe allergic dermatitis, such as cypripedium (lady's slippers), *Euphorbia*, primroses, lilies and vanilla beans; sometimes also mangoes and, in Japan, lacquer made from *Rhus vernicifera*.

Iroko dermatitis.—Idiosyncrasy to wood dust is not uncommon. Iroko is a trade name for *Chlorophora excelsa*, a tree of East and West tropical Africa, and known as African teak. The dust produces the usual signs of allergy, with skin irritation, ædema of face, blepharospasm, acute coryza and pharyngitis. Other woods, such as satin wood, teak and mahogany, also produce allergy in susceptible persons.

V. CLIMATIC SKIN DISEASES PRICKLY HEAT

Synonym.—Climatic hyperidrosis.

Prickly heat, or, as it is sometimes called, lichen tropicus, is probably a form of miliaria (not of lichen) connected with the excessive sweating incident to

the heat of tropical climates in association with high humidity. It therefore occurs especially in the Red Sea, Persian Gulf, the plains of India, in Eritrea and Somaliland; in the New World, in Panama and in northern parts of South America. Europeans are specially liable; Africans are more or less immune.

Ætiology.—According to Pollitzer, the mechanism of its production depends on the non-cornification of the cells of the stratum corneum, the individual cells of which, in consequence of being sodden by constant perspiration, swell, and so obstruct the orifices of the sweat-glands, thereby leading to accumulation of sweat in the ducts. The blebs and bulke are due to breakdown of function in the second form of sweat glands of the skin, especially the large coil sweat glands localized to the axilke and genital regions. The miliary rash, commonly known as prickly heat, is due to dysfunction of small sweat glands, and a pemphigoid condition due to dysfunction of the large sweat glands, and it is often associated with heat exhaustion (see p. 401).

Symptoms.—Many Europeans in the tropics suffer from prickly heat, particularly during the earlier years of residence. Some never seem to become acclimatized, but continue year after year to exhibit their crop of prickly-heat lesions when the hot season comes round.

Though sufficiently annoying in the robust and healthy, prickly heat is not a grave affair. It is otherwise in the invalid, delicate sickly children, hysterical and, especially, parturient women; to these it may prove, by interfering with sleep and provoking restlessness, a very serious matter.

Prickly heat consists of a miliary-like eruption, generally most profuse on those parts of the body, as around the waist, which are closely covered with clothing; but it also occurs on the backs of the hands, on the arms, legs, forehead, occasionally on the face, the scalp, in fact on any part of the surface of the body except the palms and soles. The minute, shining, glass-like vesicles, and the numerous, closely-set, slightly inflamed papules, give the skin a feeling of being thickly sprinkled with grains of sand. The eruption may continue for months on end, becoming better or worse according to circumstances. The pricking and itching are often exceedingly distressing. Anything leading to perspiration immediately provokes an outburst of this almost intolerable itching-nothing more certainly than a cup of hot tea or a plate of hot soup. As soon as the weather becomes cool the eruption and the irritation quickly subside. Horne and Mole (1949) have now made the interesting observation that prickly heat is relieved by reducing salt intake and can be made to relapse by increasing the intake of table salt. These workers (1951) have found that raised sweat chloride and decreased conductivity of heat through the skin are present in cases of mammillaria, whether the anhidrotic syndrome is present or not. The sweat chlorides begin to rise, whilst prickly heat is present before the mammillaria have become visible. Therefore a raised sweat chloride may be associated with severe prickly heat. The reduction in sweating in areas of active prickly heat has been confirmed.

Blomfield (1943) divided the forms of prickly heat clinically into (1) miliaria, (2) multiple boils, (3) impetiginous, (4) pemphigous, (5) pustular with fungous infection. A special and distinct form of boil develops, consisting of insidious, painful blisters, especially on the fingers. These are deep-seated whitish swellings, very often with paronychia. An impetiginous rash is a frequent concomitant infection.

A very severe form consists of very painful symmetrical crops of blebs and bullæ in armpits and crutch. The bullæ are filled with thin pus, and are surrounded by a bright red ring of acute inflammation.

The pemphigoid state is a late stage of the disease, and is often compli-

cated by secondary fungous infection.

Pathology.—O'Brien (1947), on histological studies, claims that a "civilized toilet" results in depriving the skin of its sebaceous secretions with the result that a keratin ring closes the orifices of the sweat ducts, so that a vesicle of sweat collects in the upper epidermis, causing a secondary reaction. The exuding sweat forms vesicles round the remains of the ducts and percolates downwards to the corium. If an area of skin is smeared with anhydrous lanoline this horny occlusion is prevented. With "lipoid response" plug-formation occurs beneath the vesicle and causes disintegration of the ducts with obstruction of the sweat flow and gives rise to a vesicular reaction deeper than that of prickly heat. This accounts for the persistent anhidrosis which follows and which may be associated with eczematous and exfoliative dermatitis. Sulzberger and his colleagues uphold the view that prickly heat and thermogenic anhidrosis are different manifestations of the same process.

Treatment.—Manifestly, the most important thing is the avoidance of all causes of perspiration—particularly the copious consumption of fluids, especially hot fluids—moderation in exercise, avoiding sea-bathing, close rooms, warm clothing, and so forth. A towel should be carried to mop up sweat. The sleeping-mattress and pillow should be covered with a finely woven grass mat, and the bed provided with what is known in the East as a "Dutch wife"—that is, a hollow cylinder, 4 ft. by 8 or 10 in., of open rattan work, over which the arms and legs can be thrown, and unnecessary apposition of sweating surfaces so avoided. A punkah at night is a great comfort. Afridol soap, containing oxymercuriotoluylate of sodium, in which mercury is in non-ionizable form, can be recommended as a preventive and a curative measure. The soap is powerfully germicidal and should be used twice daily with warm water. The lather should be left to dry on the skin for a quarter of an hour so that it can exercise its full effect, after which time it can be thoroughly washed off. When this is unprocurable, hydrarg. perchlor., 1 in 500 solution, may be used and allowed to dry on, followed by boric acid, calamine and zinc oxide in equal parts as a dusting powder. Biniodide of mercury, 1:1,000, with 1 oz. spirit (28.4 ml.), diluted with an equal quantity of water and menthol, 10 gr. (0.65 grm.), dabbed on the affected parts after bathing, and allowed to dry, is also recommended. Every bathroom in the tropics should be provided with some mildly astringent and antiseptic dusting powder. A very good one consists of equal parts of boric acid, oxide of zinc, and starch, such as Johnson and Johnson's anti-prickly heat powder. This should be freely applied, after careful drying of the skin, particularly to the axillæ, the crutch, under the mammæ in women, and between the folds of skin in fat children and adults.

As a prophylactic the frequent application of a salicylic-acid (1 dr.) and spirit (8 oz.) lotion has been advised. Pearse strongly recommended the inunction of a mixture of almond oil and lanoline in the proportion of 8 to 1. Calamine lotion, with or without hydroeyanic, or carbolic

acids (2 per cent.), relieves the itching. Inunction with lanoline is also recommended once a week. Loose-fitting "Acrtex" garments of the bush-shirt type appear to be the best to wear. Relief from symptoms is produced by pyribenzamine. a recent anti-histamine preparation.

TROPICAL CHEIROPOMPHOLYX

This name is given to vesicular eruptions on the hands, fingers or feet. In the majority of cases these are due simply to eczema; others are signs of dermatitis due to external irritants, or are toxic eruptions due to ringworm infection of the toes. Owing to the thickness of the horny layer on the hand, the vesicles cannot rupture as they would elsewhere, and remain in the skin for days like grains of boiled sago. The best treatment is calamine and lead lotion with liquor picis carbonis, and sometimes the addition of weekly doses of a quarter of a pastille of X-rays, not more than four in all.

It is claimed by Fitz-Patrick that a distinct form, endemic in tropical Africa and India, is caused by an anaërobic bacterium which attacks the palmar and interdigital aspects of the hands and the plantar aspects of the feet. A protective or pellanthum paste is soothing for the irritation. The following ointment is suitable:

Ichthyol					. gr. 15
Zinc oxide)					
Ol. oliv.	•	•	•	•	.aa 🖁 ss
Adeps. lanæ anhyd.					. 3i
Aq. calcis .					$.ad \bar{z}ss$

To be applied night and morning.

The ointment is rubbed well into the affected parts, and cotton gloves or socks are worn. In conjunction with this, resorcin soap must be used.

VI. FUNGOUS SKIN DISEASES

DHOBIE'S ITCH (TINEA CRURIS) AND PITYRIASIS VERSICOLOR

Ætiology and nomenclature.—By the lay public all epiphytic skin diseases in the tropics—more especially all forms of intertrigo— are spoken of as dhobie's (washerman's) itch, in the belief, probably not very well founded, that they are contracted from clothes which have been contaminated at the washerman's. There are many sources of ringworm infection in warm climates besides the much-maligned dhobie.

In the tropics, native children often exhibit dry, scurfy patches of ringworm on the scalp; and the skin of the trunk and limbs of adults is not infrequently affected with red, slightly raised, itching rings, or segments of rings, of trichophyton infection. In some cases these rings enclose areas that are many inches in diameter.

Pityriasis versicolor (Tinea versicolor) is also very common in the tropics. It is the usual cause of the pale, fawn-coloured, slightly scurfy patches so frequently a feature of the dark-skinned bodies of natives. On the dark-

pigmented skins of negroes, Indians and dark-complexioned Chinese, the patch of pityriasis—unlike that in Europeans and light-skinned Chinese—is usually paler than the healthy integument surrounding it. The pigment in the fungus and the profuse growth of the latter conceal, as a coat of paint might, the dark underlying natural pigment of the skin, which, moreover, in certain cases seems to be affected (either increased or decreased) by the action of the fungus. The disease is most commonly seen in young adults, is favoured by excessive perspiration, and especially by flannel underwear, and is rarely seen in the aged.

Several varieties of fungi may be involved in the production of pityriasis; besides Malassezia furfur, the best-known is Cladosporium (Dematium) mansoni, of which a culture in maltose-agar produces black hemispherical colonies, and correspondingly black patches on the affected skin. The



Fig. 121.—Dhobie's itch, symmetrical lesions in groins.

mycelium and spores are refractile with slow budding. The hyphæ are 2-3 μ , the spores 3-8 μ . Fluorescence can be demonstrated in scaly

patches by Wood's light.

The expression "dhobie's itch," although applied to any itching, ringworm-like affection of any part of the skin, most commonly refers to some form of epiphytic disease of the crutch or axilla. This infection has now become widespread in Great Britain and endemic in many English public schools, where it is spread by infected clothes and water-closet seats. The causative fungi are Epidermophyton floccosum (syn. E. cruris, E. inguinale, etc.), Trichophyton metagrophytes (syn. T. gypseum asteroides, etc.), T. rubrum (syn. T. purpureum, E. rubrum, etc.) and Nocardia minutissima of erythrasma.

E. floccosum is peculiar to man only; it is easily cultivated, but grows slowly. On Sabouraud's agar medium it takes a week to develop, and appears first as a yellowish glabrous growth with a powdery surface in which masses of the characteristic pyriform spindles are found. Subcultures tend to be cottonous and show fewer spindles.

Symptoms.—The suffering to which certain forms of dhobie's itch give rise is often severe. In hot damp weather, especially, the germs proliferate actively, producing, it may be, smart dermatitis. The affection begins usually as slightly raised, rounded and elevated papules which spread peripherally, producing a raised festooned border covered with thick scales. The excessive irritation thus set up leads to scratching and, very likely. from secondary bacterial invasion, to boils or small abscesses. The crutch. or axillæ, or both, are sometimes rendered so raw and tender that the patient may be unable to walk or even to dress. (Fig. 121.) It commonly extends backwards on the perineum and into the natal cleft about the anus. It often affects the skin under pendulous breasts and occasionally forms patches resembling tinea circinata on the thighs. The irritations thus produced are usually worse at night, and may keep the patient awake for hours. Even without treatment, when the cold season comes round, the dermatitis and irritation subside spontaneously. The affected parts then become dry. pigmented, and scurfy, and the fungus remains quiescent until the return of the next hot weather.

Diagnosis.—The diagnosis of mycotic dermatitis is usually easily made, the festooned margin is almost conclusive. If doubt exists, the microscope may be necessary; but, owing to the inflamed condition of the parts, there may be much difficulty in finding fungous elements, even when the case is certainly epiphytic. A negative result is, therefore, not always conclusive against ringworm. The mycelial elements can be distinguished in epidermal scales soaked in liquor potassæ. It has to be distinguished from seborrhæie dermatitis, intertrigo, flexural psoriasis and dhobie mark dermatitis.

Treatment.—The patient should get two pairs of running shorts, which should be worn on alternate days, the pair not in use being boiled. After a thorough use of soap and water, a preliminary soothing treatment by lead lotion, or an ichthyol or hazeline cream, is desirable.

Chrysophanic acid may be prescribed in the following form with guttapercha, and should be painted on with a brush on alternate nights.

```
Acid. chrysophan. . . . gr.xx (1·296 grm.)
Chlorof. . . . . 3i (3·5 ml.)
Liq. gutta-perchæ . . . 3i (28·42 ml.)
```

Cignolin is a synthetic chrysarobin and is useful in all fungoid skin affections. Cignolin is apparently free from toxic action on the kidneys, and in neat concentrations it can be applied to the scalp without any danger of conjunctivitis. The prescription is cadojel (a proprietary tar preparation), 1 grm.; cignolin, 0·1–0·2 grm.; benzol, 10 grm. If cadojel is not obtainable, a suitable formula is:

```
      Ol. cadin (deod.)
      ... Mxl (2·368 ml.)

      Cignolin
      ... gr.iv (0·259 grm.)

      Benzol. rect.
      ... 3i (28·42 ml.)
```

The combination of cignolin and tar follows the indications closely, for the former has a parasiticidal action and the latter is unrivalled for its soothing properties. The method of application is very simple, the affected areas being painted with the solution twice daily and then covered with strips of gauze. If there is too much irritation, then the painted areas are further protected with a thin layer of Lassar's paste or calamine lotion.

The patient should be isolated and kept in clean pyjamas during treatment. For three days cignolin, 2 per cent. in soft paraffin, is applied with bandages; even if one thigh only is affected, both should be treated. At the end of this period, only disinfected or non-infected clothing should be worn, and, as an additional precaution, unguentum acid. benz. should be applied nightly to the treated areas.

For those who cannot tolerate cignolin "Mycozol" is suitable and consists of:

Acid. salicyl	•	•				4 pe	er cent.
Chloretone	•	•		•		5	,,
Mercury salicylate	•	•	•	•	•	4	,,

in a mixture of lanolene and vaseline.

In America undecylenic and propionic acids have been found effective in all forms of tinea infections. Undecylenic acid is used in the form of 10 per cent. to 20 per cent. cream of the carbowax or lanette wax types; a dusting powder containing 2 per cent. undecylenic acid and 20 per cent. zinc undecylenate is also employed. Mixtures containing them are also effective:

Undecylenic acid					5 per	cent.
Zinc undecylenate				· .	20	••
Vanishing emulsion	base	up t	ю.		100	,,
or:		_				
Sodium propionate					16.4	,,
Propionic acid .					3.6	,,
Propylene glycol		٠.			5.0	,,
N-propyl alcohol					10.0	,,
Zinc stearate .					5-0	,,
"Carbowax 4,000"					40.0	,,
Water ad					100-0	,•

For the ringworms of the thick-skinned natives, linimentum iodi of double strength, freely applied, is the best, speediest and most efficient remedy, but it is too irritating and painful for the European skin.

Prophylaxis.—The various forms of crutch dhobie's itch may be avoided by wearing next the skin short cotton bathing-drawers and changing them daily, at the same time powdering, after the daily bath, the axillæ and crutch with equal parts of boric acid, oxide of zinc, and starch.

Erythrasma is a chronic fungous infection of the stratum corneum caused by Nocardia minutissima, characterized by superficial lesions in axillæ and genitocrural regions, but occasionally involving other intertriginous areas. It occurs throughout the world, most commonly in the tropics. The lesions appear as punctate to palm-sized circumscribed maculopapular areas which vary from light brown to reddish-brown in colour, with a serpigenous crythematous border. In scrapings of the skin the fungus appears as short, delicate, branching filam ents 1μ or less in diameter. The morphological characters distinguish it from trichophyton and Epidermophyton floccosum. The treatment is the same.

Dhobie mark dermatitis is produced by fluid from the nut of Semecarpus anacardium, the ral or bella gutti tree and is known as bhilawanol, chola gutti in Assam, and chela in India. It is used by dhobies for marking clothes for laundering. It contains strong vesicants which withstand repeated washings and causes local pruritus with dermatitis, erythema, vesiculation, and crust formation.

RINGWORM OF THE FEET (HONGKONG FOOT; ATHLETE'S FOOT; MANGO TOE; BROCQ'S ECZEMA; TINEA PEDIS)

A peculiarly intractable infection of the feet, occurring especially amongst Europeans, is commonly observed in China and is known locally as "Hongkong foot," but now has a world-wide distribution; is found in



Fig. 122.—Ringworm of the foot with allergic eczema.

schools, athletic clubs, coal mines and the services where communal bathing facilities are provided and is associated with conditions which produce hot, sweating feet. This mycotic infection, as identified by Dodd, is believed to be a variety of Epidermophyton floccosum, or, according to Beintemar, Trichophyton interdigitale or T. rubrum. It occurs especially during the summer months and appears as deep-seated vesicles about the inner margin of the hollow of the sole, or on, or between, the toes at their proximal extremities; or as a macerated condition of the skin of the interdigital clefts and of the contiguous surface. Scaling of the skin with persistent and intolerable itching is a marked feature, and it often becomes secondarily infected (Fig. 122). Often a mycotic infection of the nails

and the palms of the hands is associated with it, resembling Hebra's eczema marginatum, which is said to be due to E. floccosum. Isolation of the fungus presents difficulties owing to contaminating bacteria and moulds, but can be overcome by using potassium tellurite or penicillin to inhibit bacterial growth and by adjusting the reaction of the culture media to $pH\ 10.5$ to discourage the growth of moulds. A similar condition has been described in Turkish baths in England by Whitfield, and in swimming pools in the Southern United States, as well as among bathers in Holland. As a preventive measure the application of the following lotion is recommended:

Sulphomerthicate powder (Lilly & Co.) should be dusted into socks after bathing.

Care must be taken to distinguish dermatophytids or allergic reactions which are superimposed upon foot ringworm, especially in T. gypseum infections. Where such reaction is present treatment must be directed on other lines, trichophyton skin sensitivity tests are useful in differentiation; treatment should be directed to the relief of inflammation and fungicides should be avoided till the acute stage has subsided. Potassium permanganate 1:4,000 should be used in cases with much vesiculation and applied before and after evacuation of the vesicles.

Treatment.—The application of Whitfield's ointment, after the feet have been soaked in hot water, is recommended: salicylic acid 1, benzoic acid 1, coco-nut oil 12, soft paraffin 16 parts. This ointment must be persisted with for three weeks or more. Castellani's 1 per cent. fuchsin paint is widely recommended.

Rademacher (1948) recommended the following treatment: 25 per cent. sulphathiazole in talc is dusted on to the lesions daily. Definite improvement appears within forty-eight hours. A commercial preparation consists of 5 per cent. sulphathiazole in a bland ointment and has been found satisfactory. All infected areas should be covered with a film of the powder. The criterion of cure is the healing of all lesions and disappearance of adherent cutaneous débris. In refractory cases 10 per cent. of powdered sulphathiazole is made up with 2 per cent. salicylic acid ointment. The course of treatment lasts from two weeks to one month.

Other authorities favour azochloramide in triacetin, 1 in 500. This penetrates some distance into the tissues and thus enables the germicide—azochloramide—to extirpate the deeper filaments. This preparation N—N—dichloroazo-dicarbonamidine, is a complex chlorine compound, which liberates chlorine slowly. Carbon tetrachloride may also be effective.

Mycil dusting powder (BDH) contains chlorphenecin, tale, zinc and boric oxides. Sopronol ointment is composed of sodium propionate, proprionic acid, sodium caprylate, zinc caprylate and dioctyl sodium sulphosuccinate and is recommended. Mersagel (Glaxo) is a fungicide

jelly containing phenyl mercuric acetate (1 in 750). Another is Merthiolate cream, and also tincture of merthiolate, a solution of merthiolate in spirit, which sinks deep into the affected skin and thereby kills off the spores

of the fungus.

For eczematous complications the toes should be separated by strips of gauze, and the foot should be covered with it and kept constantly wet with glycerine of lead subacetate, 1 oz., glycerine, 1 oz. and water to 1 pint. This lotion can be later replaced by Lassar's paste. If a staphylococcal infection is present, dressings of acriflavine, 1 in 20,000, should be applied.

As an after treatment Macleod recommended bathing or paddling in

sea-water.

Infected patients should take careful precautions against the spread of the fungus, and should wear special slippers in the bathroom, and the feet should be dusted with 1 per cent. salicylic acid in talc. Loofah soles and bath towels are recommended as they can be sterilized by washing.

As a measure against re-infection the patient may wear cotton toe-caps. which must be boiled, and he should also have a rubber bath-mat for exclusive personal use. Shoes and woollen socks must be sterilized by formol vapour.

RINGWORM OF THE NAILS (Tinea Unguium)

This is a mycotic infection of the nails and is a comparatively common and extremely intractable condition in Europeans, especially in India and China; it may last for twenty years or more. It may occur as an independent affection, or secondary to ringworm of the skin, scalp or beard. and is often found in association with tinea cruris. One or all of the nails of both hands and feet may be attacked. The fungus is a trichophyton, usually T. rubrum or T. metagrophytes.

The fungus first attacks the epidermis of the nail-bed and gradually invades the nail matrix. In doing so it causes considerable discolouration, ridging and fissuring of the nail itself, which becomes opaque, with a brittle. frayed edge. The fungus may pass from the skin over the nail-fold and in

this manner reach the matrix.

Diagnosis.—The appearance of the affected nail is not sufficiently characteristic to be distinguished without microscopic examination. The disease is generally well advanced before it can be recognized. For microscopic diagnosis, scrapings of the nail are boiled in liquor potassæ, or left to soak for twenty-four hours. The scrapings themselves should be made as thin as possible with a piece of glass. The fungus can then be recognized in the softened nail débris, especially in small dark hæmorrhagic spots. The diseases liable to confusion with ringworm of the nails are eczema, syphilis and, especially, psoriasis.

Treatment.—In the early stages, when the lunule is attacked, the disease may be stamped out by softening the affected portion with solution of potash, and painting with tincture of iodine or with a 2 per cent. solution of corrosive sublimate in alcohol, twice daily. When the nail is completely involved, cure is almost impossible save by extirpation or by avulsion. The result is, however, disappointing, as the new nail usually becomes

infected in turn. After removal, the thickened nail-bed should be scraped, and the matrix dressed with a parasiticidal ointment:

Fuchsin paint is also effective.

The shedding of the nails by application of X-rays is unsatisfactory. Less severe cases are treated by softening the nail-plate by wearing rubber finger-stalls containing soft soap for a few days; the softened nail is then scraped down as far as possible with glass, followed each time by the application of lint soaked in Sabouraud's iodine (iodine 5, potassium iodide 1, water 100), which should be kept in position by a loose rubber finger-stall.

Mycosis of the Ear (Otomycosis)

Mycosis of the external auditory meatus is popularly known as "Panama ear," "Surfer's ear," "Hot weather ear," or otitis externa diffusa, and more descriptively as "desquamative external otitis." According to Davis (1948) the majority of cases show a coexisting fungous infection of other parts of the body. The infection declares itself by soreness and redness of the external auditory meatus, with tenderness on contact and pain on chewing. The external canal is coated with a moist, soft, sebaceous-like detritus. In the third stage the walls become swollen so that the canal is obliterated. The pain produced is worse at night and there is moderate pyrexia. Fungous mycelium and spores can be demonstrated in the detritus (Aspergillus niger and A. flavus), but numerous other fungi have also been described. For treatment the ear is syringed out and swabbed with spirit. Glycerine and ichthyol (10 per cent.) tampons are inserted. Subsequently the canals are daily swabbed with spirit and painted with carbol-fuchsin paint. Other authorities use 5 per cent. suspension of mercuric chloride in liquid paraffin as drops. Excoriations are treated with ammoniated mercury ointment.

TINEA IMBRICATA

Synonym.—Tokelau Ringworm.

Geographical distribution.—The affection is principally met in the Eastern Archipelago and in the islands of the South Pacific, where it affects a large proportion of the population. It has been found to extend westwards as far as Burma, and northwards as far as Formosa and Foochow on the coast of China. Cases have been reported from Central Africa and the interior of Brazil. Once introduced, it spreads very rapidly in countries with a damp, equable climate and a temperature of 80–90° F. Very high or very low temperatures and a dry atmosphere are inimical to its extension.

Ætiology.—On detaching a scale and placing it under the microscope, after moistening with liquor potassæ, a trichophyton-like fungus can be seen in enormous profusion. The parasite evidently lies between epidermis and rete, and by its abundance causes the former to peel up. As the fungus does not die out in the skin travelled over, it burrows under the young epithelium almost as soon as the latter is reproduced. Hence the peculiar concentric scaling and the persistence of the disease throughout

the area involved. When the scales are washed off by the vigorous use of soft soap and hot water, the surface of the skin is seen to be covered with brownish parallel lines—evidently the slightly pigmented fungus

proliferating and advancing under the young epidermis.

The parasite, said to be of two varieties, Trichophyton concentricum (svn. Endodermorbuton concentricum) and T. indicum, can be cultured by immersing the scales in alcohol for five to ten minutes and then placing them, one scale to each tube, in glucose broth. After five or ten days the scales, if uncontaminated. are transferred to solid media, and growth takes place in three or four weeks.

Symptoms.—Tinea imbricata may at first be confined to one or two spots on the surface of the body; usually, in a short time it comes to occupy a very large area. It does not generally affect the soles and palms. although it may do so; nor is the scalp a favourite site. Baker remarked that it avoids the crutch and the axillæ. With these exceptions it may, and commonly does, sweep over and keep its hold on almost the entire surface of the body, so that after a year or two a large part of the body is covered with the dry, tissue-paper-like scales, arranged in more or less confused systems of concentric parallel lines. This arrangement of the scales is absolutely characteristic of the disease (Plate XVIII).

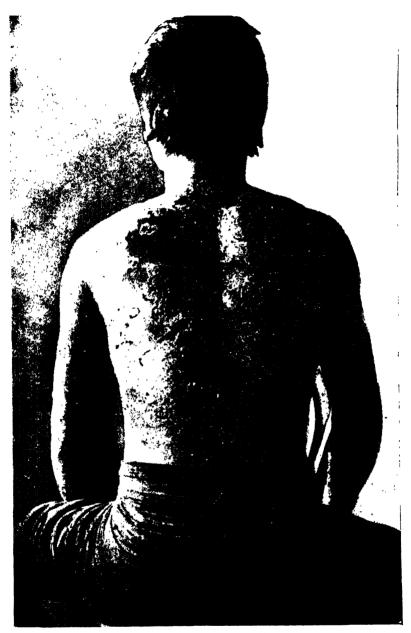
An inoculation experiment readily explains the production of the scales. their concentric parallel arrangement, and the mode of extension of the patches. About ten days after the successful inoculation of a healthy skin with tinea imbricata, the epidermis at the seat of inoculation is seen to be very slightly raised and to have a brownish tinge. Presently the centre of this brownish patch—perhaps a quarter of an inch in diameter—gives way, and a ring of scaling epidermis, attached at the periphery, but free, ragged, and slightly elevated towards the centre of the spot, is formed. In a few days this ring of epidermis has extended so as to include a larger area.

The scales, if not broken by rubbing, may attain considerable length and breadth; but, of course, their dimensions are in some degree determined by the amount of friction to which they are subjected. Usually, they are largest between the shoulders—that is, where the patient has a difficulty in scratching himself. The lines of scales are from \(\frac{1}{2} \) to \(\frac{1}{2} \) in apart.

Diagnosis.—From ordinary ringworm, tinea imbricata is easily distinguished by the absence of marked inflammation or congestion of the rings, by the abundance of the fungus, by the large size of the scales, by the concentric arrangement of the many rings or systems of rings, by the non-implication of the hair, and by the avoidance of crutch and axillæ. From ichthyosis it is distinguished by the concentric arrangement of the scaling, by the peripheral attachment of the scales, and by the presence of an abundance of fungus elements.

Treatment.—The best treatment for tinea imbricata in natives is the free application of linimentum iodi; its action is said to be increased by the addition of salicylic acid, 15 gr. to the ounce. Limited patches may be treated with chrysophanic acid ointment (20 gr. to the ounce), or by the more modern preparation, cignolin. Clothes should be boiled or burned.

Prophylaxis.—Daniels related that tinea imbricata is a comparatively rare disease in Tonga, and the natives attribute this to their custom of



TINEA IMBRICATA

(By permission of Medical Department of Sarawak Government.)

PLATE, XVIII

oiling the body with coco-nut oil. Since the Fijians adopted this practice the disease has become somewhat less prevalent among them. Personal cleanliness, and the immediate and active treatment of any scaling spot, should be carefully practised in the endemic countries. Amongst certain Central African tribes it has never been observed in women, who oil their bodies, whereas the men, who do not adopt this custom, are subject to the disease.

In Tahiti the use of chrysophanic acid is now general among the natives; as a consequence, the disease is less prevalent there than it was only a few years ago.

VII. SPIROCHÆTAL SKIN DISEASE AND AFFECTIONS OF THE HAIRS

PINTA

Synonyms.—Caraate; Mal del Pinto.

Definition.—A spirochætal disease characterized by peculiar pigmented patches on the skin. "Pinta," a Spanish word to describe spotted or mottled appearance, was first used by Oviedo (1505–1516).

Geographical distribution.—Pinta occurs in certain districts in tropical America, especially along the river banks—in Mexico, Venezuela, Colombia, Bolivia, and in one or two places in Peru, Chile, Guatemala, Honduras, and Brazil.

Ætiology.—For many years this peculiar skin disease was regarded as due to parasitic fungi. Menk (1926) on the high percentage of positive blood Wassermanns suggested that it was a spirochætal disease. Saenz, Armenteros and Triana in Cuba (1938) found spirochætes in the skin abrasions, and Blanco (1938) obtained them by lymph gland puncture. To this spirochæte the name of S. herrejoni was given. This discovery was confirmed by Blanco (1938) in Mexico, by Iriate in Venezuela (1939) and by Léon in Ecuador, who found the organisms especially abundant in the early papules. Brumpt (1939) proposed the name Spirochæta (Treponema) carateum. There has been some confusion about the correct terminology, but it is now considered that the name Spirochæta carateum, as proposed by Brumpt, has priority.

This spirochæte, in measurement as well as in appearance (by dark-ground illumination), is closely allied to S. pallida. When first isolated it

is very active, but its motility decreases in about twenty minutes. It is 12 to 18 μ in length, and easily stained by silver impregnation and by Giemsa stain. It is readily dissolved by saponin and dies in a short time in bile (Fig. 123).

Varela claimed that S. carateum has certain differences from most other spirochætes.

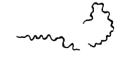


Fig. 123. Spirochæta carateum (herrejoni). (After Leon y Blanco.)

When stained by Giemsa it has a flexible cylindrical form with pointed ends. The turns are 0.6–1 μ in width, 0.4–0.5 μ deep and 9–10 in number.

Animal inoculations.—The Venezuela Commission reported that inoculations in guinea-pigs, rabbits and rats were without result.

Varela and Olarte have shown that antibodies are present against

S. carateum in the serum of pinta patients. There is no cross immunity between pinta and syphilis. Thus syphilitic chances may be seen in



Fig. 124.—Pinta, vitiliginous form, from Ecuador. (Dr. L. A. Léon, Quito.)

pinta subjects, and pinta can be transmitted to syphilitics. Attempts to inoculate pinta subjects with yaws have been partially successful. Nevertheless antibodies against S. carateum are present in the serum of syphilitics.

Inoculations. Human -Blanco (1940) demonstrated, by inoculation into volunteers, that the disease is infectious and may be easily transmitted when a small amount of serum from a pinta lesion is injected. In syphilitic patients an initial papule developed, but the secondary eruption was atvpical. Positive Wassermann reactions were obtained, but not before the appearance of the secondary eruption. The primary lesion differs from that of syphilis or yaws in that it is always closed and does not ulcerate. Experimental inoculations showed that previous syphilis does not give absolute immunity to pinta.

Pathology.—The spirochetes are chiefly located in the Malpighian cells, especially in small areas of acanthosis in the epidermis. A greater involvement of the corium has been described in pinta than in yaws, but much less than in syphilis.

Spirochætes may be demonstrated in lymph obtained from glands near the lesions. The hair follicles and portions of the sweat glands are surrounded by inflammatory cells. The pigmentary function is specially affected in pinta, and scanty pigment granules may be seen inside the cells of the stratum germinativum; they are also present in other cells of the Malpighian layer and in the melanophores of the dermis.

PINTA 685

Symptoms.—There are two periods in the development of pinta: the primary phase and that of generalization. The incubation period in experimental inoculations varies from 7–20 days, by which time an initial papule appears. This extends peripherally as a squamous, reddish patch, reaching a diameter of 1 cm. in a month, and then continues to spread peripherally. Secondary lesions appear in crops around the primary papule, spreading to other parts in about five months. Psoriasis-like, trichophytoid and linchenoid types are recognized. Progressive hyperpigmentation is then observed; later still, depigmentation, which gives rise to various colours, or vitiliginous spots, ranging over the body. The colour of the lesions in order of frequency appears to be blue, white,



Fig. 125.—Hyperkeratosis of soles of feet in pinta. (Dr. L. A. Léon, Quito.)

mixed, lead-coloured, violet, black, red or yellow. The spots vary in size and in shape: round, oval or irregular. They are not elevated, but are always strikingly visible (Fig. 124). The most marked subjective symptom is pruritus.

In natural infections the primary lesion is usually on an exposed part, particularly the legs and feet and arms, extending to the hands and face. According to Blanco, the initial lesion is never seen on the palms, or on the trunk. Modern observers divide the disease into three distinct stages, showing different clinical, serological and immunological features.

The primary stage occupies the period when the initial lesion is present and lasts from five months to one year. The secondary stage is characterized by skin lesions or papules which are rapidly converted into erythematous squamous lesions (named pintids) and ensues five months to one year from the time of infection. In the tertiary, or dyschromic, stage there are achromic or pigmentary spots, erythema, keratoderma and superficial atrophy. Super-infections may be produced by inoculations at this stage. Hyperkeratosis of palms and soles, as in yaws, are to be regarded as late manifestations (Fig. 125), but according to Mazzotti these are not found in Mexico, but may be due to a superinfection with yaws. Eosinophilia and

an increase of basophil cells occur in a high percentage of cases. Oncho-

gryposis, or pigmented changes in the nails is frequent.

The exact relationship of pinta to syphilis is further complicated by the fact that Sænz in Cuba found arritis, aneurysm and enlargement of the diameter of the heart and valvular lesions in 23.3 per cent. The association of this skin spirochætosis with visceral syphilis is of course conceivable.

Diagnosis.—The characteristic spirochætes are present in the lesions, but obviously it is impossible to differentiate them in their morphology from S. pallida or S. pertenuis. Pinta is often associated with syphilis and yaws lesions, such as juxta-articular nodules. Sænz found changes in the cerebro-spinal fluid in 10 per cent. (increased globulin content and colloidal gold curve).

Depigmented, or vitiliginous, areas are common in tertiary yaws and syphilitic lesions in the coloured races to which pinta is almost entirely limited. It is obvious that many other skin diseases have in the past been confused with pinta. Apparently too many examinations have been made for the presence of fungi and micro-organisms without proper cleansing

and disinfection of the skin.

Oteiza (1945) has described a reaction, by injecting the serum of early cases intradermally into the forearm of volunteers. An erythematous spot formed in from six to sixty-one days, about the size of a pin's head, often with satellite papules. Spirochætes were subsequently demonstrated in the lesions.

Differential diagnosis has to be made from leprosy, yaws, syphilis, erythrasma, pityriasis versicolor and other epiphytic skin diseases, and also from plain vitiligo or leucoderma.



Fig. 126.—Human hair (magnified) affected with Trichosporum beigeli.

Treatment.—The modern treatment for pinta is neosalvarsan, bismuth preparations and penicillin as described for yaws. The superficial skin lesions yield rapidly to salvarsan, but the atrophic vitiliginous spots remain unaffected, as in yaws. The Wassermann reaction in a proportion of cases remains positive after disappearance of the lesions. Oral administration of aureomycin causes the disappearance of S. carateum from the interstitial fluid obtained by pressure of the skin after excoriation of the epidermis (Mazzotti and Olarte, 1949).

TRICHOSPOROSIS

Synonym.—Piedra.

The black piedras are found in South America, chiefly in Brazil, Paraguay, Ecuador, Argentina, Uruguay, Colombia, etc. The small black nodule on the hair shaft is the ascostioma of the fungus Piedraia hortai belonging to the Asterinex, a family of fungi parasitic on the leaves of trees in very humid climates. The nodules consist of tightly packed stroma of dark-brown hyphæ 4–8 μ in diameter; when crushed, asci containing fusiform curved ascospores are revealed. The white piedras are more widely distributed, being found in various countries of South America, Africa, Southern Asia, Japan and parts of Europe. The multiple white nodules on the hair are formed of sclerotial masses of the mycelium of the fungus Trichosporum beigeli and other species, which are related to the common fungi known as Geotrichum, Oidium or Mycoderma. In contrast to black piedra this white form attacks chiefly the coarse hairs of the body (Figs. 126, 127).

Microscopically, the nodules, which are not so discrete as in black piedra, consist of a mass of polygonal cells, yellowish-green to brown,

with a definite cell-wall. The cells of a mycelial thread are separated from one another by thick black cell-walls, between which there is little intercellular substance.

The hyphæ tend to be perpendicular to the surface of the hair and segment into round or oval cells, $2-4~\mu$ in diameter. Budding cells (blastospores) are also seen in the mycelial mass. Colonies of T. beigeli on Sabouraud's medium develop at room temperature and appear first as a cream-coloured, slimy growth which is soft in consistency.

Treatment. — The affected hair should be bathed twice daily with a lotion consisting of 1 dr. of formalin to 6 oz. of rectified spirit, reinforced by 2 per cent. sulphur ointment. The affected

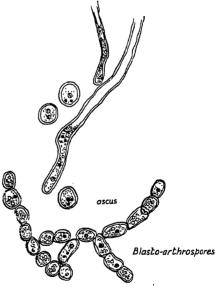


Fig. 127.—Fungus elements of T. beigeli.

surrounding skin should be rubbed with mercurial ointment.

Trichomycosis

Synonyms.—Trichonocardiasis; Trichomycosis axillaris.

Trichomycosis is a fungous disease of the hair which in many ways resembles piedra. It may produce skin irritation and stain the clothes. The shafts of the hairs, more especially those in the axilla, are attacked.

Trichonocardiosis axillaris is common in many parts of the world, including England. It is caused by *Nocardia tenuis*, which produces a hard mucilaginous substance in which pigment-forming cocci vegetate, causing the distinctive black, red, and yellow varieties. *N. tenuis* is difficult or impossible to culture.

Treatment.—Consists of bathing with formalin and spirit and applying

mercurial ointment.

VIII. SKIN DISEASES CAUSED BY ANIMALS THE CHIGGER, OR SANDFLEA

This insect, formerly confined to the tropical parts of America (30° N. to 30° S.) and to the West Indies, appeared on the West Coast of Africa for the first time about the year 1872. Since that date it has spread all over the tropical parts of that continent, and even to some of the adjacent islands—Madagascar, for example. As a cause of suffering, invaliding, and indirectly of death from secondary infections, it is an insect of some importance. It is now extremely prevalent on the East Coast of Africa, and is causing a large amount of invaliding among the Indian coolies there by whom it has been introduced into India

there by whom it has been introduced into India as far east as Karachi, but in no other part.

The chigger (*Tunga penetrans*) is not unlike the common flee either in appearance or, with one

The chigger (Tunga penetrans) is not unlike the common flea either in appearance or, with one exception, in habit. It is somewhat smaller (1 mm.), the head being proportionately larger and the abdomen deeper than in the flea. It is red or reddish brown. Like the flea, its favourite haunt is dry, sandy soil, the dust and ashes in badly kept native huts, the stables of cattle, poultry pens, and the like. It greedily attacks all warm-blooded animals, including birds and man. Until impreg-

Fig. 128.—Chigger, impregnated female. × 10. (Blanchard.)

nated, the female, like the male, is free, feeding intermittently as opportunity offers. As soon as she becomes impregnated she burrows diagonally



Fig. 129.—Section of female chigger in the stratum lucidum of the skin. (Fülleborn, Arch. für Schiffs-und Tropenhyg.)

into the skin of the first warm-blooded animal she encounters where, being well nourished by the blood, she proceeds to ovulation. By the end of this process her abdomen, in consequence of the growth of the eggs it contains, has attained the size of a small pea. (Figs. 128, 129.) As seen in Fig. 129, the chigger within the epidermis enters the stratum lucidum, which it invades and pushes before it. The epithelial layer becomes attenuated. The parasite becomes anchored in the corium by means of chitinous excresences which stick out into the surrounding tissues. The first anterior and the two posterior segments do not participate in the enlargement, the latter acting as a plug to the little hole made by the flea on entering the skin. When the eggs are mature they are expelled by strands of muscular fibres which intersect the abdomen. They fall on the ground and, according to Hicks, the larva hatches on the third or fourth day; the first moult occurs on the fifth to eighth day

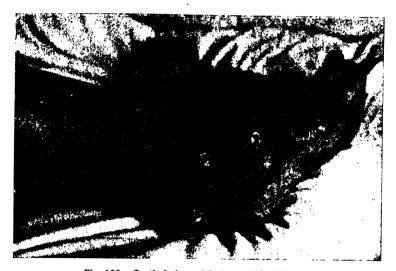


Fig. 130.—Septic lesions of foot caused by chiggers.

and preparation for pupation on the sixth to seventeenth days. The larva pupates at the same time, and the imago usually emerges about the seventeenth day. (See also Appendix p. 1070.)

During her gestation the chigger causes a considerable amount of irritation. In consequence of this, pus may form around her distended abdomen, which now raises the inflamed integument into a pea-like elevation. After the eggs are laid (according to some, before this process) the superjacent skin ulcerates, and the chigger is expelled, leaving a small sore which may be infected by some pathogenic micro-organism, such as the bacterium of phagedæna or of tetanus, with grave consequences. (Fig. 130.)

The chigger is not a good jumper and therefore she seldom attacks the skin above the dorsum of the foot.

The soles (Fig. 131), the skin between the toes, and that at the roots of the nails are favourite situations. Other parts of the body are by no means

exempt; the scrotum, the penis, the skin around the anus, the thighs, and even the hands and face, are often attacked. Usually only one or two chiggers are found at a time; occasionally they are present in hundreds, the little pits left after their extraction, or expulsion, being sometimes so closely set that parts of the surface may look like a honeycomb.

Ulceration is common, and may follow removal of the chigger or natural extrusion of the egg-sac. The ulcer commences as a tiny pit and, as it extends, the sloping edge may develop into a septic ulcer. It remains more or less circular in outline, except under the nail or nail margin, where the



Fig. 131.—Chiggers in sole of foot. (Dr. C. W. Daniels.)

outline is more irregular and a pocket of pus forms underneath it. Chronic absorption of pus may lead to thrombophlebitis.

Treatment.—In chigger regions the houses, particularly the ground floors, must be frequently swept and accumulations of dust and débris prevented. The housing of cattle, pigs, and poultry demands the same precautions. The floors should often be sprinkled with carbolic water, pyrethrum powder, D.D.T., or similar insecticide, and walking bare-footed must be avoided. A daily bath must be taken, and any chiggers that may have fastened themselves on the skin at once removed. They may be killed by pricking them with a needle, or by the application of chloroform, turpentine, mercurial ointment, or similar means, after which they are

expelled by ulceration. The best treatment, however, is not to wait for ulceration, but to enlarge the orifice of entrance with a sharp, clean needle and neatly to enucleate the insect entire. Some native women, from long practice, are experts at this little operation. The part must be dressed antiseptically and protected until healed. Europeans living in an endemic district should wear high boots. A daily inspection of the feet, especially under the nails, is advisable. Should any black dot be discovered, the chigger should at once be removed.

Prophylaxis.—If avoidable, camps should not be formed in chigger-infested spots or in the neighbourhood of native villages. The camping-ground should be swept or, if necessary, fired: the floors of huts and tents may be sprayed with insecticides and naphthaline, and native tobacco

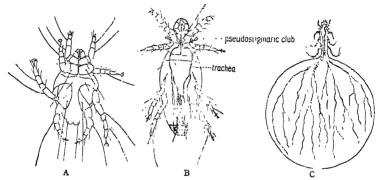


Fig. 132.—Pediculoides ventricosus. × 80. (After Alcock.) A, Male; B, adult female; C, pregant female with brood-sac.

dusted inside boots or shoes. Balfour recommended that the feet be rubbed thoroughly with a mixture consisting of 5 drops of lysol, or liq. cresoli sap., in 1 oz. of vaseline. Special attention should be paid to the interdigital clefts. Pigs should not be kept in the vicinity of dwelling-houses, as these animals are severely attacked by chiggers.

ACARINE DERMATOSIS

Several forms of mites inhabiting sugar, grain, or copra may live as temporary parasites on the skin of man, and set up an intense irritation not unlike that produced by scabies. One of the most familiar of these is "grocer's itch," set up by mites of the genus Glycophagus, which are common in raw sugar and cause an erythematous rash. Among the copra workers in Ceylon and the Pacific islands a similar skin affection is due to Tyroglyphus. "Grain itch," an urticarial and papular eruption of the exposed parts of the body, is caused by Pediculoides ventricosus (Fig. 132, A, B, C) in those who handle grain, cotton-seeds, or beans. These mites give rise to a severe pruritus. Preventive treatment consists in the application of 5 per cent. beta-naphthol ointment, and dilute carbolic acid to kill the mites.

NUÑEZ ANDRADE'S DISEASE

A parasitic dermatitis resulting from the bites of the larvæ of Neoschönaastia nunezi in Brazil. Molluscoid lesions are accompanied by internal pruritis. This insect, 0.33-0.45 mm. in length, is a common parasite of fowls.

BUTTERFLY AND MOTH DERMATOSES

Leger, Mougels and Bozé have described urticaria, conjunctivitis and facial cedema due to contact with a saturniid moth, Hylesia urticans, in French Guiana. In Celebes similar lesions are evoked by another moth Scirronhaga innotata. The dorsal side of the wings of this moth are

covered with a greyish-white powder which is the irritating agent.

Le Gac and colleagues describe a similar dermatitis due to another moth, Anaphe renata. The imago and the larvæ are clothed with detachable irritating hairs. Africans as well as Europeans are affected in French Equatorial Africa. Similar moths occur also on the Gold Coast. Caterpillar dermatitis is provoked by the hairs larvæ of many kinds of butterflies and moths. In Brazil, especially, flannel moths (Megalopygidæ) are well known. In New Guinea and N. Australia the species is Ochrogasta contraria (Bercovitz).

Section VIII.—LOCAL DISEASES

CHAPTER XLIII

TROPICAL PYOMYOSITIS—RHINOSPORIDIOSIS—RHINO-SCLEROMA—AINHUM—BIG HEEL—ONYALAI—CHIUFA— TROPICAL EOSINOPHILIA

I. TROPICAL PYOMYOSITIS

Synonyms.—Myositis Purulenta Tropica; Tropical Myositis; "Bungpagga" (Patton).

History and geographical distribution.—In 1912 H. H. Scott described this disease in Jamaica. Deep intramuscular abscesses were associated with pyrexia, and a striking feature was the hard swellings set up by enormous collections of serous fluid. A small bacillus was isolated, which was named B. serofaciens.

In the same year Külz found intramuscular abscesses very common in the Cameroons; and in Duala, in 1907–1908, out of 386 natives, 18 were operated on for intramuscular abscesses, and out of 86 Europeans, 5 were thus treated. In natives abscesses were multiple; in Europeans usually single, and they varied in size up to that of a hen's egg. He believed that they were secondary to Loa loa infection.

In 1913, Wise and Minnett in British Guiana described what was obviously the same condition, and they failed to find remains of adult filariæ (Wuchereria bancrofti) in the pus, though filaria embryos were discovered in seven. Recurrence of abscesses in the same patient was a feature of the disease. In most instances streptococci were isolated from the pus.

P. A. Buxton (1928) published a very complete account of myositis as he observed it in Samoa, and was convinced on atiological grounds that myositis is distinct from the deep suppuration sometimes observed in filariasis. It is of considerable importance in Samoa, and was observed in Europeans, Samoans, half-castes, Chinese, and Melanesians. He found that pulmonary complications were not infrequent, abscesses were invariably intramuscular, suppurative and non-suppurative lesions were common, while Staphylococcus aureus was the organism responsible.

Atiology.—The infection was regarded by Pawan as secondary streptococcal and staphylococcal infection in filaria-infected subjects. Grace thought that the causal organism was a hæmolytic streptococcus derived from the throat. Von Bormann thought that the organism was a hæmolytic staphylococcus, usually S. aureus, less commonly S. albus. Erasmus in East Africa found the former most frequently. In the Editor's experience these two organisms are responsible, though occasionally Streptococcus pyogenes is found.

The site of entry is uncertain, but dissemination appears to take place by the bloodstream, for the lymphatics and lymph glands may show no sign of inflammation.

Associated infections.—Pyomyositis is more apt to occur in persons who are debilitated as the result of some other longstanding infection. In the Editor's experience this has been either ancylostomiasis, malaria, and, in a proportion, syphilis. In his series of cases the Wassermann reaction was positive in 50 per cent. One of the chief aims of treatment should be the eradication of these

concomitant infections, and, wherever necessary, antisyphilitic treatment with salvarsan and bismuth should be instituted.

Symptoms.—Several types may be distinguished.

Acute non-suppurative stage.—An indurated, tender, ill-defined mass can be felt in the affected muscles where the patient complains of pain. There is usually slight pyrexia, with inflammatory reaction over the neighbouring tissues and pitting ædema. On incision the tissues are ædematous, whilst the regional lymph glands are usually enlarged and tender.

Acute suppurative stage.—The clinical features are those of a deep-seated abscess, and, on incision, large collections of pus in the affected muscles are evacuated. The abscess cavity is loculated, requiring a wide incision and the breaking down of septa formed of dense indurated muscle, or fibrous tissue. The numerous sloughs in the cavity are characteristic. These abscesses occur in widely separated sites: in the thigh muscles, pectoralis major, serratus magnus, latissimus dorsi, gastrocnemius, flexor muscles of arm, iliopsoas and internal oblique. Generalised septicæmia may result.

Chronic abscesses have been recorded in the adductor magnus.

Diagnosis.—The diagnosis of pyomyositis should not present any great difficulty, but it has to be differentiated from gummatous suppuration, filarial abscesses, glanders, melioidosis, rheumatic nodules and swelling, osteitis of femur, cold abscesses of sacro-iliac joint, septic mastitis, perinephric abscess and fibrosarcoma.

Treatment.—Under modern conditions treatment consists of essential surgical incisions and the administration of a sulphonamide—sulphadiazine by choice—by the mouth. Vigors Earle (1946) has proved the efficacy of penicillin by injection of 2,000 units two-hourly up to 11 doses. No doubt in future penicillin treatment will be adopted wherever pyomyositis occurs.

II. RHINOSPORIDIOSIS

Definition.—A disease due to a yeast-like organism, Rhinosporidium seeberi¹, which infects the mucous membrane of the nose, producing nasal polypi and tumours on the cheek, conjunctiva, lacrymal sac, uvula, ear, glans penis and skin.

History.—R. seeberi was first described in Argentina (1896), and considered to be a protozoon allied to Coccidium. Subsequently it was found in nasal polypi by O'Kinealy in 1903, when the organism was described by Minchin and Fantham. Ashworth (1923) thought that the organism is probably a yeast, or phycomycete. F. Allen (1936) has written the most complete account based on a study of sixty cases.

This parasite has now been recorded from India, Ceylon, Argentina, Paraguay and Uruguay, Uganda (Mowat and Hennesey, 1941), and the United States.

Ætiology.—Rhinosporidium seeberi (Wernicke, 1903) is a spherical or oval non-motile organism which occurs in polypoid growths, usually lying between the connective-tissue cells. The earliest stages are about 6 μ in diameter, with a chitinous envelope, vacuolated cytoplasm, and vesicular nucleus containing a karyosome (Fig. 133, A, B). When fully-grown, the cyst, or sporangium, may measure 0.25–3 mm. in diameter, but when half-grown the nucleus commences to divide by binary fission, until thousands are produced, of which the majority become daughter-spores, though a considerable proportion remain unchanged. The fully-formed sporangium (Fig. 133, c) finally bursts and discharges the spores, which are enclosed in chitinous envelopes; they then spread into the connective tissues via the lymph channels, and on reaching suitable spots the trophic stage at once begins and the cycle is repeated.

¹Recently some authorities have expressed the view that R. seeberi is in reality a protozoon.

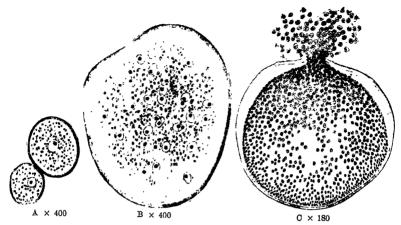


Fig. 133.—Rhinosporidium seeberi. (After Ashworth; by permission of Roy. Soc. of Edin.)

A, Trophic stages. B, Section of a stage with 64 nuclei, 24 of which lie in this section. C, Sporangium from which spores are being discharged, accompanied by mucoid substance, through a wide orifice. The first spores to issue (those near the opening) are followed by the central spores. The peripheral spores lie in a fairly firm mucoid matrix. Stretching of the envelope, due to growth of the sporangium, has not only reduced its thickness, but has almost caused the disappearance of the thickness annulus round the pore.

Attempts at cultivation proved partially successful in Ashworth's hands, and multiplication of the spores took place, but slowly, on Sabouraud's medium.

The mode of transmission of this parasite is undetermined, but the occurrence of a closely related organism, R. equi, in the nasal cavities of the



Fig. 134.—Rhinoscleroma of two years' duration in an Egyptian woman. (Dr. H. K. Giffen.)

horse is suggestive. Ayzar in India has found it in the noses of cattle (1925).

Allen (1936) has figured multiple pedunculated tumours on the nose and face generally and has described one case in particular with secondary tumours on both feet which ultimately became distributed over the whole body.

Treatment consists in removing the polypi from the nares by a wire snare. Medical treatment does not appear to be indicated, although Wright reported that the tumours disappear after intravenous injections of tartar emetic. Allen (1936) used neostibosan though it is not always effective. A popular native remedy is a snuff composed of tobacco leaves and lime.

III. RHINOSCLEROMA

Rhinoscleroma (Scleroma respiratorium) (Fig. 134) is a well-marked disease in all its aspects, pathological or bacteriological. It has a world-wide distribution, but at the present day is much commoner in the tropics than elsewhere. It takes the form of spontaneous, painless, and exceedingly chronic inflammatory growths occurring at any place in the respiratory passages from the nostrils to the hilum of the lung. Gross deformity of the nose, or narrowing or distortion of the respiratory passages results. Sometimes there is perforation of the nasal septum with total destruction of the uvula. The process extends along the respiratory passages with little change in the surrounding tissues; on the whole, it tends to form

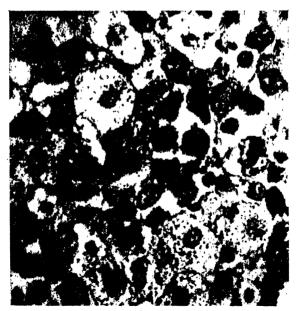


Fig. 135.—Rhinoscleroma: Photomicrograph of tissue, showing Mikulicz cells and general histological picture. (Dr. H. K. Giffen.)

metastases with enlargement of the neighbouring lymphatic glands, but, in spite of this, the general health and condition remain unaffected.

Geographical distribution.—Rhinoscleroma is spread over widely distributed regions in special nests, or foci, but occurs all over the world. The most extensive region is in Eastern Europe, in Hungary, Poland, the Ukraine and the northern shores of the Black Sea and Caspian. Other foci have been noted at Tomsk in Siberia, in Turkestan, Bengal, Java, Sumatra, central and southern France, Morocco, Egypt, North America (in New England states), Cuba, Mexico, Panama, Colombia, Brazil, Peru, and Chile.

Actiology.—The cause of rhinoscleroma is undoubtedly Bacterium rhinoscleromatis described by V. Frisch in 1882. It is closely related to Streptococcus pneumoniæ, and is usually Gram-negative. It is easily cultivated, and forms knob-like colonies on gelatin or agar, greyish on the whole, and less conspicuous than S. pneumoniæ. It usually coagulates milk, and forms acid freely with lactose. In sections, it is found in hard fibrotic swellings in the nose, scattered throughout the mucosa and submucosa. It has so far been found impossible to reproduce the lesions by inoculation, either in man or animals. In fact, it exhibits a very low order of pathogenicity for laboratory animals, with the exception of mice.

It has to be differentiated from other encapsulated pneumococcus-like organisms in the nose.

Pathology.—Rhinoscleroma is characterized by a peculiar form of plasma-cell infiltration of great density, and by gaps or "fat-cells," which are found to consist of swollen cells with foamy cytoplasm ("foam-cells" or "Mikulicz cells") (Fig. 135). Very frequently, also, there are hyaline-drops or Gram-positive "Russell's bodies," which occur in all kinds of degenerative tissues, and are probably derived from the plasma cells. The rhinoscleroma nodule is known as plasmoma (Unna); it never breaks down, but becomes progressively sclerosed.

Treatment.—The treatment is mainly by plastic operation to remove the unsightly outgrowths.

Various other methods, the most important of which is X-ray therapy, have been tried. Intravenous injection of tartar emetic, as in schistosomiasis or ulcerating granuloma, has been advocated by some. It is a curious fact that complicating febrile diseases, such as erysipelas, typhoid or typhus fever, may cause healing of rhinoscleromatous growths. This has led to a trial of inoculated malaria or protein-shock therapy, with encouraging results.

IV. AINHUM (SPONTANEOUS DACTYLOSIS)

This is a very peculiar disease affecting the toes, particularly the little toes, of negroes, East Indians and other dark-skinned races, both in the Old and the New World. The name, derived from the Naga dialect, means "to saw or cut." A recent important contribution is that by Kean and colleagues (1946) in a clinical summary from Panama of 45 cases during a forty-year period. The disease occurred in adult active and otherwise healthy West Indian negro males, the incidence being 1.5 per 10,000. Tidy has described ainhum of the toes in three members of a Lebanese family from Beirut. Findlay has described pseudo-ainhum as due to nerve damage.

Symptoms.—The disease commences as a narrow groove in the skin, almost invariably on the inner and plantar side of the root of the little toe or little finger. Sometimes it may be bilateral. The association with hyperkeratosis palmaris was first noted by Spencer in 1942. It may occur in one foot only, or in both feet simultaneously, or it may affect one foot after the other. The groove, once started, deepens and extends gradually round the whole circumference of the toe. As it deepens—perhaps, though not necessarily, with ulceration—the distal portion of the toe is apt to swell to a considerable size, as if constricted by a ligature (Figs. 136, 137). There may be no pain, but Kean asserts that it may be pronounced and progressive. There is inconvenience from the liability to injury to which the dangling and now everted toe or finger is exposed. In the course of years the groove slowly deepens, and finally the toe drops off, or is amputated. The groove may or may not correspond with a joint. In rare instances, after the two distal phalanges have dropped off, or been amputated, the disease recurs in the stump, and the proximal phalanx in its turn is thrown off. Of the other toes, the fourth is the one which is most frequently affected;



Fig. 136.-Ainhum.



Fig. 137.—Ainhum at its height. (Dr. A. B. Filho.)

very rarely is the third, second or great toe attacked. In the Army Medical Museum at Washington, U.S.A., there is a wax model representing a case of this or a similar affection, in which all the toes had been thrown off and the disease was making progress in the leg.

Occasionally, the terminal phalanx of the fifth digit of the hand has been affected. No relationship to leprosy, yaws, scleroderma or syphilis has been noted.

Ainhum of the fingers should be known as keratoderma hereditarium mutilans (Vohwinkel).

Ainhum is very rare in women or children, being most common in adult males. It runs its course in from one to ten or even more years.

On section, it is found as a rule, though not invariably, that the panniculus adiposus of the affected toe is much hypertrophied, that the bone is infiltrated with fatty matter, and that the other tissues are correspondingly degenerated. Sometimes the bone is thinned, or even altogether absorbed. At the seat of constriction a line of hypertrophy of the epithelial layers, and of atrophy of

the papillary layer of the skin, together with a band of fibrous tissue, more or loss intimately connected with the derma, surrounds, in whole or in part, the narrow pedicle.

Treatment.—It has been suggested that division of the constricting fibrous band would delay the evolution of the disease. In the early stage this might be tried. When troublesome, the affected toe should be amputated. It is said that the application of salicylic ointment delays the process in the earlier stages (Moreira).

V. BIG HEEL, OR ENDEMIC HYPERTROPHY OF THE OS CALCIS

Maclean described a peculiar form of enlargement of the os calcis which he observed at Kaziankor, Gold Coast, among Fantis and Kroos. The disease begins somewhat suddenly, being preceded by fever, and attended by pain and tenderness which reach their maximum in about a month, gradually diminishing during the succeeding one or two months. Concurrently with the pain there is a swelling of the external surface of the os calcis, rarely of the other tarsal bones.

Maxwell reported a similar condition in natives of Formosa. As in Maclean's cases, the patients were young adults from twenty to twenty-five years of age.

VI. Onyalai (Essential Thrombocytopenia)

Under this title Massey and, later, Wellman (1904) originally described a peculiar disease occurring among the natives of Portuguese West Africa. Since then it has been recognized in East Africa, Tanganyika, on the Congo, and in Northern Rhodesia, where it is known as "Chilopa," "Kafindo," or "Akembe," (bleeding disease—Wallace). It is not usually seen outside Africa, though Preston Maxwell, in 1901, described a somewhat similar condition in the Fokien region of South China. It is characterized by formation of a number of vesicles, distended with blood, from $\frac{1}{2}$ to $\frac{3}{4}$ in, in diameter, on the hard palate and on the inside of the cheeks. Some of them are unbilicated. They differ from ordinary blood blisters by the presence of numerous trabeculæ and by the semicoagulation of the contents which makes the vesicle difficult to empty. Occasionally it is accompanied by fever and, although Massey's original cases, with one exception, recovered within a week or ten days, natives regard the disease with dread, owing to its reputation for deadliness.

The majority of victims are young adults. The onset is sudden and the early symptoms are lassitude, general dullness, and suffusion of the conjunctivæ. with pyrexia, sometimes of 103-104° F. There is tenderness over the parotids and vague pains. These are soon s cceeded by widespread hæmorrhages into the skin and mucous membranes. In natives the cutaneous hæmorrhages are most easily seen in the axilla. Stein and Miller remark the constant association of cutaneous purpura, which is easily missed on black skins. Bullæ are seen on the lips, buccal mucosa, tongue, and palate, the last-named in particular. Epistaxis occurs in practically every case and subconjunctival hæmorrhages are in evidence. Bleeding occurs from the bowels as well as from the bladder. At autopsy hæmorrhagic vesicles are found in the serous membranes, the pleura, peritoneum and diaphragm. A common finding is hæmorrhagic bronchopneumonia. Usually there are large retroperitoneal perirenal hæmorrhages. Blackie found involvement of the central nervous system in one of his cases. The bleeding time is increased, and there is a reduction in blood platelets. Normoblasts may be present. The blood sedimentation rate is slightly increased. Blackie thought that onyalai is an acute form of essential thrombocytopenia due to defective nutrition. Stein and Miller (1943), who carried out a fine piece of work, found that onyalai is not confined, as had been thought, to native races. It is quite common in the Transvaal and Northern Bechuanaland. In Africa it extends from the equator to 26° south latitude, Johannesburg being the most southerly point. They studied 21 cases which could be classified as mild, severe or acute. The youngest patient was a native female aged 7 months. Hæmorrhagic bulke are peculiar to onyalai, and not found in other forms of thrombocytopenic purpura, suggesting some toxic factor. The course of the disease is aggravated by the menses in women, and response to treatment is similar to the acute incipient episodes of idiopathic thrombocytopenic purpura.

Van den Berghe states that the erythrocytes may be reduced to 800,000 per c.mm., leucocytes to 3,600 and blood platelets to 5,600 per c.mm. Normoblasts

are usually numerous.

The diagnosis has to be made from snake-bite, in which hæmorrhagic symptoms

may supervene.

Blackie found that the most effective treatment was by blood transfusions and by injection of 18 ml. of donor's blood intramuscularly into the buttocks or outer aspects of the thighs, but Stein and Miller found the intravenous route better. They suggest that splenectomy is indicated in patients who relapse after this treatment.

VII. CHIUFA ("CHINKUMBI" AND "KANYEMBA")

This is a disease resembling acute gangrenous rectitis described in the earlier editions of this manual, which has been reported from South America. Gilkes described cases he had under his care in Northern Rhodesia. It is found in the Luangwa and Lusenfwa valleys at an altitude of 2,000–2,500 feet. Its onset is sudden and it runs an acute course. The primary manifestation is stated to be a white powdery condition which appears round the anus and gives the appearance of "boracic acid or flour"; in women it covers the vulva as well. After a few days this disappears and the patient becomes acutely ill with pains in back and neck and a temperature of 104° F. The anus becomes relaxed and the rectum can be seen protruding, red and angry. Throbbing in the rectum is noted, and constipation is the rule. The inflammation travels up the large intestine until the colon is involved, when there may be diarrhea and vomiting. In women the vagina also may be affected.

VIII. TROPICAL EOSINOPHILIA (PULMONARY EOSINOPHILOSIS)

Under the name of pseudotuberculosis of the lung, with massive eosinophilia, a new entity was described by Frimodt-Möller (1940) and Weingarten (1943) in India, but has now been found in Ceylon, North West and Central Africa, Tanganyika, China, the Philippines, Samoa, S. United States and other places. This is characterized mainly by spasmodic bronchitis, leucocytosis and high eosinophilia. It affects mostly people who live by the sea, and has apparently no relationship to any other disease, but is thought to be a form of allergy. physical signs are those of bronchial asthma. Males are more often affected than, females. The common age is from twenty to thirty. Preliminary symptoms are cough, lassitude, dyspnœa on exertion, heaviness or pain in the chest palpitations; occasionally hæmoptysis (Visvanathan). There is usually considerable loss of weight (Menon). During the febrile periods the spleen is moderately enlarged. The most striking feature is massive eosinophilia, which accounts for the considerable leucocytosis up to 60,000 per c.mm. It may reach 90 per cent. and is higher than in any other disease, except eosinophilic leukæmia. The E.S.R. is raised in 75 per cent. A positive Paul Bunnell reaction often occurs. According to Viswanathan an acute and a chronic type can be recognized. X-ray shows disseminated mottlings in the lung, the average single focus being the size of a split pea, somewhat similar to silicosis. The pathology is essentially

eosinophilic bronchitis and bronchiolitis. There are dark reddish-brown areas scattered over the surface of the lungs. The most striking lesions are tubercle-like nodules with groups of giant cells in the centre and clusters of surrounding monocytes. Differentiation of tropical eosinophilia, according to Weingarten, from asthmoid bronchitis and Löffler's syndrome, is as follows: In the first there is no leucocytosis, and only moderate eosinophilia without pulmonary infiltration, whilst in the second the clinical and radiological signs disappear rapidly and spontaneously. It has a seasonal incidence, occurring in temperate climates as well as in the tropics. Cold agglutinins are present in the serum in high titre (Visvanathan, 1949). Tropical eosinophilia is usually benign and lasts for years, but reacts to intravenous injections of neoarsphenamine in courses of six doses of 0·15 to 0·45 grm. Exacerbation of symptoms and increase of eosinophile count occurs after one injection of 0·15 grm. neoarsphenamine.

Mapharside may also be given in the same doses and acetylarsan in six weekly injections of 0.45 grm. Stovarsol, or carbarsone, is also beneficial when given

by the mouth in 4 gr. tablets thrice daily for 7-10 days.

Löffler's syndrome, originally described in Switzerland, is often mistaken for pulmonary tuberculosis (Freund and Samuelson, 1940). The cause is unknown. Engel in China (1936) and Koino in Japan ascribed it to allergy from privet blossoms, but this has not been observed elsewhere. It resembles pulmonary coccidioidomycosis (see p. 627), to some extent sarcoidosis of the lung, and bronchial asthma associated with periarteritis nodosa.

The discovery by Carter and his colleagues (1944) of mites (Tyroglyphus and Carpoglyphus) in the sputum of pulmonary eosinophilosis has not been confirmed. Another genus, Pneumonyssus, is definitely pathogenic in the lungs of monkeys. In South Africa Ordtmann (1946) has described an epidemic of allergic asthmadue to sewage files (Psychoda) affecting workers in a sewage farm. Sensitivity

to extracts made from the flies was proved by allergic skin tests.

An allied condition is Eosinophilic erythredema, a syndrome previously unknown, which occurred in Palestine (1945), where it has been described by Klopstock and Steinitz. It was characterized by the appearance of red swellings, infiltration of the skin and mucous membranes, which are transient and occur over wide areas, associated with an eosinophilic leucocytosis. It occurs at all ages and in both sexes and is obviously allergic in nature.

An entirely new aspect has been given to this subject by the work of W. F. Aitken (1953), who has brought forward evidence that the cause of tropical eosinophilia is a virus which occurs in groups, or in families, in close association. There is also some evidence that it is spread by fæces in insanitary surroundings.

Section IX.—ANIMAL PARASITES AND ASSOCIATED DISEASES

CHAPTER XLIV

PARASITES OF THE CIRCULATORY SYSTEM: SCHISTOSOMIASIS (BILHARZIASIS)

Definition.—A group of diseases caused by certain digenetic trematodes of the family Schistosomidæ which inhabit the venous system of man in various tropical and subtropical countries.

I. Genito-urinary Schistosomiasis (Schistosoma hæmatobium), or Bilharziasis

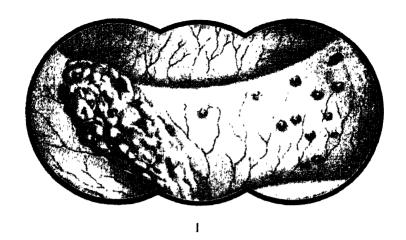
Synonyms.—Bilharziasis; Bilharzia Disease; Endemic Hæmaturia.

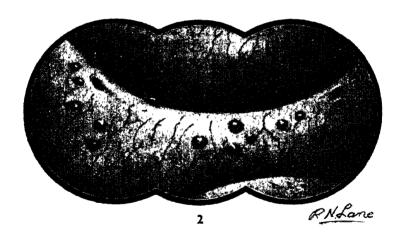
Definition.—A chronic endemic disease produced by infection of the pelvic veins, particularly those of the bladder, and occasionally those of the rectum, by *Schistosoma hæmatobium*, the eggs of which, being deposited in the mucous membrane, give rise to hæmaturia, cystitis or other symptoms connected with the urinary organs, and occasionally, when deposited in the rectum, to muco-sanguineous discharges from the bowel. The eggs of the parasite are discharged in the urine and, in certain cases, in the fæces.

Geographical distribution.—The eggs of this parasite were identified by Harley in Natal in 1864, and since then the disease has been found in other parts of Africa, more particularly along the eastern side of the continent, as far south as Port Elizabeth, and it is common throughout the Union of South Africa, especially in Natal. In Central Africa it occurs in the Northern Sudan, Uganda, the Congo, Rhodesia and in North Abyssinia; it is met with in West Africa as well, especially in Liberia and Sierra Leone. In North Africa it is especially common in Morocco, Algeria, Tunis and Egypt. It also occurs in Arabia, parts of Palestine near Jaffa, Persia, Iraq, Cyprus, in the town of Tavira in Portugal, in Mauritius, Réunion, and Madagascar. A few indigenous cases were reported, over forty years ago, from Western Australia. (Map VII.)

Precise information about the ravages of schistosomiasis in Egypt are forth-coming. Scott, as the result of 40,000 examinations, found that in the northern and eastern edge of the Delta, reaching as far as Cairo, 60 per cent. of the inhabitants are infected with S. hæmatobium, and an equal number with S. mansoni; in the apical southern half of the Delta, however, though still 60 per cent. are infected with S. hæmatobium, only one-tenth of that number have S. mansoni. The line between the first and second areas is sharp and defined, and does not correspond to any noticeable topographic, hydrographic or demographic variation. Moreover, there appears to be no difference in the number of planorbis snails, the intermediary hosts of S. mansoni, in these two regions. In the northern two-thirds of that part of the Nile Valley between Cairo and Assiut, S. hæmatobium infects 50 per cent. of the population, but S. mansoni and the planorbis snail are absent. In the southern third, where old basin irrigation—

¹ An endemic focus of urinary schistosomiasis has been found in the Ratungui district of Bombay State by Gadgil and Shah (1952). The ova are terminal-spined and resemble those of S. hæmatobium.





Bilharzial disease of the bladder before treatment, and one month after treatment with sodium antimony tartrate. The yellow nodules in Fig. 1 are the dead ova working their way through into the bladder cavity. They do not indicate active bilharzial disease.

(By permission of Brit. Journ. Surgery, Ogier Ward and Dr. J. B. Christopherson).

SCHISTOSOMIASIS OF THE BLADDER

PLATE XIX

that is irrigation at flood Nile—takes the place of the new perennial irrigation, S. $h\varpi matobium$ alone is present, but infects only 5 per cent. of the population. Heavy infection with S. $h\varpi matobium$ is associated with perennial irrigation from high-level canals, which takes the place of flood irrigation, with alternate flushing and drying. In the district, where 5 per cent. of the inhabitants are infected with S. $h\varpi matobium$, 1 in 1,000 die from this infection: in the Northern Delta district, this proportion rises to 1 in 22.

Ætiology. Parasite.—Schistosoma hæmatobium (Fig. 254. A & B.) is a unisexual trematode. The male measures 1-1.5 cm. in length by 1 mm. in breadth; its cylindrical appearance is due to the infolding of the two sides of the body to form a gynæcophoric canal. The female, darker, but longer, 2-2.5 cm. in length, is partially enclosed in the gynæcophoric canal of the male. Some parasites live in the blood of the portal vein and its mesenteric branches, but the majority dwell also in the pubic, vesical, and uterine plexuses. The longevity of this parasite is phenomenal, as it may remain active and produce viable eggs for more than thirty years.

The eggs are oval, and are provided at one end with a definite spine. They measure 0·16 mm. by 0·06 mm. Normally they are voided in the urine, exceptionally in the fæces. It has been pointed out by Khalil that the hatching of the egg in water is due to osmotic pressure. A 0·75 per cent. salt solution completely inhibits this process. It has been generally supposed that the provision of a spine was designed to facilitate the passage of the egg through the blood-vessel wall, but probably, as Kohlschütter and Koppisch have pointed out, the spine merely facilitates the adherence of the ova to the wall. The ovum plays an entirely passive part, but the endothélial lining is the more active factor, followed by an inflammatory reaction which fixes it in situ. Only ova which are laid in blood vessels close the bladder pass to the outside, whilst all others are trapped in the tissues. These observations have been confirmed by Torres in lesions produced in the armadillo.

Life-history.—On coming into contact with water, the eggs hatch and give rise to an active, ciliated embryo or miracidium, which, as a rule, enters a freshwater snail, usually of the genus Bulinus; in the liver, or hermaphrodite gland, of this molluse it develops into sporocysts, eventually into active, bifid-tailed cercariæ which, on escaping from the snail, re-enter man by burrowing through his skin. Some cercariæ pass through the lung capillaries to the heart and are distributed all over the body, including the skin. Many are held up and die, giving rise to a secondary cutaneous reaction with wheals and blotches due to breaking down of cercariæ. Those which get to the mesenteric capillaries of the bowel wall reach the portal system where they grow until almost sexually mature and become paired. They then return against the stream to the mesenteric veins to lay eggs. (For further details regarding the life-history of this parasite, see p. 945.)

Pathology.—The changes brought about by this schistosome vary very much according to the degree and duration of the infection (Plate XIX). In almost every case the walls of the urinary bladder are early affected. All that may be apparent to the naked eye at this stage is a certain amount of injection of the small vessels of the mucosa vesicæ, and certain exceedingly minute vesicular or papular elevations of the surface of this membrane. When these minute elevations are examined microscopically they are found to contain eggs, even in minute blood-vessels. Later, especially in the trigone of the bladder, there are rounded patches of inflammatory thickening which project somewhat, are granular on the surface, and dense; on section they creak under the knife as if they contained gritty particles. It is evident that these elevated, thickened patches are the result of an inflammatory process provoked by the clusters of eggs which

the microscope reveals scattered throughout their entire extent. The eggs are principally deposited in the submucosa, less extensively in the mucous membrane, still less abundantly in the muscular walls of the organ or in its subserous connective tissue. They tend to occur in groups, each of which is invested with a connective-tissue capsule; or they may be lying in small bloodvessels which they occlude. Some eggs are seen to have undergone calcification; others are still fresh, either segmenting, or already containing a miracidium. On the surface of the rounded patches already mentioned, phosphatic deposits, also containing eggs, are not uncommon; from their yellow glistening appearance they are known as "sandy patches," and sometimes they present minute sloughs. (Fig. 138.) Besides these indurated patches, various forms of polypoid excrescence—sometimes ulcerated—may protrude from the mucous surface into



Fig. 138.—Section of bladder-wall, showing eggs of Schistosoma hæmatobium in tissues.

the cavity of the bladder. These various hyperplasiæ frequently contain the adult parasite as well as eggs. Ferguson and others described a nodular form of schistosomiasis, an affection of the subperitoneal surface of the bladder, which closely resembles tuberculosis.

In addition to what may be designated the specific changes in the mucosa, the muscular coats of the bladder are generally hypertrophied. In consequence of this, as well as of the ingrowth of villosities and different forms of new growth, the capacity of the organ may be much diminished. Its mucous surface is generally coated with a sanguineous mucus containing myriads of eggs. Gravel or small stones—generally phosphatic—are sometimes found either embedded or lacunæ in the hypertrophied and roughened bladder-wall, or free in the cavity. Not infrequently a similar hyperplasia occurs in the ureters, and particularly towards their lower ends, even at an early stage. Gelfand and others have shown that often the lower third of the ureter is dilated with thickening of the walls. In rare instances the pelvis of the kidney is affected. Stricture of the ureter, both

from small stones and from thickening of the mucous membrane, not intrequently results; this leads to dilatation of the pelvis and atrophy of the parenchyma of the kidney. It is easy to understand how, in time, these changes in the bladder and ureters may give rise to hydronephrosis, pyelitis, abscess of the kidney, and similar secondary affections. Hyperplasia of the prostate due to infiltration with eggs is sometimes found.

Hyperplasia from schistosomal infection may also occur in the vesiculæ seminales, penis, walls of the vagina, and cervix of the uterus, leading to corresponding bloody, egg-containing discharges. In Southern Rhodesia thickening and papillomata of the female urethra, periurethral abscess, scarred and fibrous ovaries containing numbers of eggs, and lesions of the Fallopian tubes, mesosalpinx, and broad ligament have been reported. The body of the uterus is not usually affected, but eggs have been found in the endometrium. In the vagina the disease may be primary or an extension from the bladder. In the vulva papillomatous masses closely resemble the confluent type of condylomata lata of syphilis, whilst the clitoris and external meatus may be destroyed and give rise to epithelioma of the vulva.

Schistosome eggs in small numbers have been found in the liver, in gallstones, in the heart, and in the kidneys, and occasionally in the brain, spinal cord, and lungs, conjunctiva and skin. Tumours of schistosomal origin have sometimes been met in connection with the peritoneum and ligaments of the uterus. The eggproduction of S. hæmatobium is slower than that of S. mansoni. The schistosomes get to the lowest branches of the mesenteric veins, some even to the rectum, when eggs may appear in the fæces, but most migrate through the hæmorrhoidal vein to the venous plexus of the bladder. Gelfand has shown how they are distributed by arterio-venous anastomoses. When the eggs are deposited eosinophil cells are attracted and may produce micro-abscesses, forming pseudotubercles on the peritoneal surface of the bowel with resulting connective tissue. If they occur on mucous surfaces they take the form of small erosions or ulcers. Giant cells form and may completely absorb the egg.

The eggs can be conveniently demonstrated in the tissues by digesting selected portions in 3 per cent. potash solution.

Symptoms.—The symptoms produced by S. hæmatobium vary in degree within very wide limits. In the vast majority of cases the patient experiences no trouble whatever; in other instances suffering is very great. Indirectly, from the serious lesions of the urinary organs to which it may give rise, this schistosome is an occasional cause of death.

Early toxic symptoms, such as pyrexia with urticaria, have been noted, and may come on four weeks after exposure to infection. A recent interesting discovery is that of eggs of S.hæmatobium in skin papules, during the stage of invasion, on the lower chest, upper abdomen, scrotum and perineum (Black, 1945). Similar skin lesions were described by Madden and Girges many years ago. The incubation period of definite disease varies from three months up to two and a half years. The cercariæ, on penetrating the skin, produce an irritative dermatitis as in other forms of schistosomiasis. (See p. 670.)

The most characteristic symptom of the presence of the parasite in the wall of the bladder is the passage of blood at the end of micturition, with or without a sense of urinary irritation. The quantity of blood passed and the degree of irritation are increased by exercise, by dietetic indiscretions, and by all such causes as are calculated to induce or aggravate cystitis. As a rule, it is only the last few drops of urine that contain blood; sometimes,

however, the hamorrhage is more extensive, and then the entire bulk of the urine may be blood-tinged. Occasionally, clots are passed.

If, in a case of moderate infection, the urine be passed into a glass and held up to the light, minute flocculi or coiled-up mucoid-looking threads will be seen floating about in the fluid. If it be allowed to stand, the flocculi, and perhaps minute blood-clots, will subside to the bottom of the vessel; these, on being taken up with a pipette and placed under the microscope, will be found to contain, besides blood-corpuscles and catarrhal products, large numbers of the characteristic terminal-spined eggs.

In doubtful cases, where eggs are few, the best way to find them is to get the patient to empty the bladder and to catch in a watch-glass the last few drops of urine which can be forced out by straining; these invariably



Fig. 139.—Section through nucleus of urinary calculus containing eggs of S. hæmatobium.

contain eggs. A low power of the microscope suffices, and is best for diagnosis. Davis in South Rhodesia has remarked upon the peculiarities of the "bilharzial facies," which becomes triangular in outline, with sunken cheeks and prominent malar bones. He considers that this appearance forms a good indication of the disease.

A case of voluntary infection with S. hæmatobium has been described by Barlow and Meleney. Over 200 cereariæ, derived from eight different specimens of Bulinus truncatus were applied at different dates over a period of three weeks. Red papules surrounding the penetration were observed on the following days. Some 76 days from the major exposure slight evening fever was recorded and

terminal-spined eggs were found in the seminal fluid. On the 78th day similar eggs were found in a plug of mucus in the fæces and on the 106th they appeared in the urine, whilst on the 139th an itching nodule appeared in the scrotum and on puncturing it ova of S. hæmatobium were demonstrated, and on the 149th a pair of adult worms were found in a nodule in the left groin. From the middle of the fourth month onwards eggs appeared in increasing numbers in the seminal fluid, fæces, and urine. The peak was reached in the sixth month in the seminal fluid, in the fæces in the tenth, and in the urine between the eighth and ninth months. It was estimated that between 20,000–30,000 eggs were passed daily in the urine. Symptoms and signs increased until the seventh month then the temperature rose to 104° F. and fell after severe sweats to normal with weakness and prostration.

Pain is by no means always predominant; when it occurs it is generally a dull sense of oppression in the suprapubic region, deep-seated perineal pain, or scalding on micturition. Frequency of micturition is an early, and urgency a very common symptom. Rectal symptoms, with passage of blood and mucus, may co-exist with the urinary symptoms, and digital examination may detect ulceration above the prostatic lobes. This localized lesion may be due to S. hæmatobium alone, though mixed infections of S. hæmatobium and S. mansoni are very common, especially in the Nile Valley. Sometimes adult worms in copula are passed in the urine; this generally occurs after a copious hæmorrhage from a ruptured vessel. Gelfand and Barnett have described a peculiar form of retention with overflow and incontinence in the male African. There are three stages—a short period of progressively increasing difficulty in micturition with

some retention, followed by complete retention with overflow for several days, and a final third stage in which the patient passes urine in increasing amounts till function is completely restored.

Endemic hæmaturia lasts for months or years. Spontaneous recovery is rarely complete. In ordinary cases, provided no re-infection takes place, the hæmaturia tends to decrease, although eggs may continue for years to be found in the last few drops of urine passed. In severe cases, sooner or later, signs of cystitis supervene and give rise to a great deal of suffering. Not infrequently the eggs become the nuclei for stone, and symptoms of urinary calculus are superadded (Fig. 139). Sometimes the pathological changes induced by the parasite in the bladder lead to new growth, in which event the symptoms become more urgent and the hæmaturia excessive. Hypertrophy, contraction, and even dilatation of the bladder are not unusual. Besides the bladder symptoms there may be signs of prostatic disease, or of disease of the vesiculæ seminales, causing spermatorrhœa. In the latter case, eggs may be detected in the semen. In other instances the ureters and kidneys become involved, resulting in ureteric dilatation and hydronephrosis. Secondary infection of the urinary tract with septic cystitis commonly supervenes. From the suffering attending these aggravated forms of infection, the patients become anæmic. wasted, debilitated, and a ready prey to intercurrent disease.

Milton pointed out the extreme frequency of urinary fistula in Egypt, the result of schistosome disease of the urethra. These fistulæ may occur anywhere in the neighbourhood of the genitals, but are especially common in the perineum and posterior surface of the scrotum, and originate from

infiltration by eggs of the pubic tissue or roof of the urethra just in front of the bulb, the eggs of the parasite being deposited in the mucous or submucous tissue. Stricture of the urethra is by no means uncommon, especially when fistulæ are connected with the floor of the urethra. In the male, infiltration of the penile sheath may result in an elephantoid condition with chordee and actual obstruction to the urinary flow. (Fig. 140.)

Makar showed that schistosomiasis of the cord and epididymis is by no means uncommon, and is determined by the anatomical peculiarities of the anastomoses between the mesenteric and internal spermatic veins, and, it may be, between the pelvic venous plexuses and deferential veins. The tunica and testes are rarely affected. The onset is very



Fig. 140.—Urinary schistosomiasis: pseudo-elephantiasis of penis, due to infiltration by ova. (After Madden.)

gradual, and it occurs in young adults, whose attention is drawn to the swelling. The cord may be nodular and covered with lentil-like bodies, or it may be enveloped in a single big mass; the term "bilharzial rosary"

well describes the condition. Cytoscopy, sigmoidoscopy, X-rays and complement-fixation tests may be needed for diagnosis, or to differentiate the lesions from somewhat similar swellings due to filariasis, tuberculosis and syphilis. In massive infiltration, the testes may have to be removed; in the early stages medical treatment is effective.

The majority of infections of schistosomal disease of the spermatic cord are due to S. hæmatobium. The following figures are given by Makar: infection with S. hæmatobium, 38 per cent.; with S. mansoni, 27 per cent.; mixed infection with S. mansoni and S. hæmatobium, 35 per cent.

Makar has reported one case of primary schistosomal disease of the gall-bladder, giving rise to duodenal stasis. The interior of this viscus was studded with sandy patches similar to those seen in the urinary bladder.

Charlewood and colleagues refer to the frequency and distribution of lesions due to S. hæmatobium in the pelvic organs of S. African women, whilst Gelfand in S. Rhodesia found that they are commonly associated with the eggs of S. mansoni in 30 cases: most commonly in the vagina, cervix, uterus, ovaries and less so in the Fallopian tubes. In the female urethra, according to Gilbert, the disease is an extension from the bladder with similar tissue changes producing thickening, ulceration of the mucous membrane and small papillomata which, emerging from the external meatus, may be mistaken for urethral caruncles. Periurethral abscesses may also form. Although the uterus is not usually affected, fibrosis of the ovaries and occlusion of the Fallopian tubes are common, so it is small wonder that in the female this disease causes sterility.

Vaginitis and cervicitis are also produced by this parasite. Papillary growths and ulcers may be mistaken for carcinoma. On the vulva, papillomatous masses containing schistosome eggs are common. Similar excrescences about the anus, in the groin and perineum can be distin-

guished from venereal warts by microscopical examination.

Pulmonary schistosomiasis (Egyptian Ayerza's disease).—In 103 cases of urinary and intestinal schistosomiasis diagnosed in Cairo 49 pulmonary complications were revealed. The first grade consists of focal arterial changes: the second of widespread arterial with slight cardiac changes: the third widespread arterial changes with gross heart involvement. It is necessary to associate these changes with both species of schistosomes; as Kenawy has pointed out, the ova of both cause a similar arteritis of the pulmonary arterioles, but in the case of S. mansoni this is invariably associated with hepatic cirrhosis. This widespread obliteration of the pulmonary arterioles at times produces a marked rise of blood pressure, hypertrophy of the right ventricle, and finally right heart failure. It is stressed that cyanosis only makes its appearance as a terminal event and that secondary lung infections are complications.

The X-ray appearances are distinctive and show what is known as the bilharzial cor pulmonale, enlargement of the right side of the heart with the shape of mitral configuration. There may also be a triangular shadow in the right hilum due to enlargement of the right branch of the pulmonary artery. There is often a diffuse and fine mottling of the lungs, due to bilharzial tubercles, which resemble

miliary tuberculosis.

According to Erfan, schistosome eggs are rarely to be found in the sputum, but according to Pyper this is more easily effected if a twenty-four hour specimen of sputum is digested for one hour in an equal quantity of 4 per cent. K.O.H. and then centrifuged.

Recently Meira and colleagues have discovered several cases of pulmonary schistosomiasis in São Paulo in Brazil.

Large numbers of eggs, as pointed out by Turner, may be deposited in the lungs, where they give rise to a form of interstitial pneumonia. Mainzer stated that in S. hæmatobium, as well as in S. mansoni infections, latent pulmonary involvement is usually present, even in the absence of pulmonary symptoms, and that by use of X-ray films the lesions can be verified about three months after infection and the sclerosis of the pulmonary arteries can be detected. Eggs have been found also in the brain and spinal cord, thus accounting for epileptic and paralytic symptoms from which the patients had suffered, but these supervene only in hyper-infected individuals. One case of schistosome myelitis was described by Day and Kenawy, with the customary symptoms. At autopsy eggs of S. hæmatobium were demonstrated in the lumbar enlargement of the cord.

Eye.—Schistosomal lesions of the conjunctiva have now been described by Badir (1946). This interesting condition appears to be rare. The majority were suffering from urinary symptoms as well. Swellings of the palpebral conjunctiva of the upper lid, yellowish pink masses between the inner margin of the limbus and the semilunar fold extending upward into the fornix have been described. The most curious feature was the discovery of the adult worms lying in a dilated vein (branch of the superior ophthalmic vein) in the region of the caruncle. Eggs of S. hæmatobium have been found in granuloma of the conjunctiva. It is an open question how the adult parasites reach the conjunctival tissues.

Chesterman found certain districts in the Congo where eggs which appeared at first to be S. hæmatobium are found only in the fæees, giving rise to dysenteric symptoms closely resembling those produced by S. mansoni, but in this instance they are longer and with more attenuated extremities than those usually seen in the urine (see Appendix, p. 949). Similar conditions have been recorded from the Assiut district of Egypt, where only S. hæmatobium is present.

Fisher, at the instigation of Chesterman, brought forward a considerable amount of evidence that this Congo schistosomiasis is not due to S. hæmatobium as was thought, but to S. intercalatum, a species which in its morphology is intermediate between that of S. hæmatobium and S. bovis. The spindle-shaped eggs resemble those of the latter species and also of S. matheei, with terminal well-developed spine, which may attain a length of $20~\mu$. The intermediary host appears to be Physopsis africana. Zellweger found this species commonly in Gaboon, along the course of the Ogowé river and its tributaries. This discovery has been confirmed by Schwetz.

The symptoms produced by S. intercalatum appear to be mild; in Yakusu (Congo) it has been found that 50 per cent. of the school-children are infected; their health is not seriously affected, but sometimes spleen and liver are enlarged. Dysenteric symptoms and abdominal pain constitute the only outward signs of the disease, and pulmonary manifestations (in contrast to S. hæmatobium) are practically absent. Toxic manifestations, which usually accompany massive infections with S. mansoni, or S. japonicum, have been noted. (Fig. 141.) The hepatic and intestinal symptoms run a similar course, with uricaria and bronchial asthma. The infected bowel, as seen by sigmoidoscopic examination, has a granular appearance suggesting sandpaper, and there are petechiæ of minute size, but no polypi or ulcers.

Schistosomal appendicitis, due to accumulation of S. hæmatobium eggs in the appendix, is a clinical entity. Lovett Campbell, in Northern Nigeria, found them



Fig. 141.—Schistosomiasis of the Congo with splenomegaly. (Dr. C. C. Chesterman.)

in 57 per cent. of all appendices removed at operation, and considers that this infection may produce symptoms requiring urgent surgical intervention. Barsoum, on the other hand, stated that it does not cause or predispose to appendicitis of the inflammatory type.

Diagnosis. — The diagnosis of this disease is not difficult; the presence of eggs in the urine is decisive. (Figs. 142, 143.) In countries like Egypt, where the disease must often concur with chyluria, with stone. with vesical tumour, with gonorrheal cystitis, and with pyelitis, as well as with prostatic disease, care must be exercised in each particular case to separate the special factors to which the various symptoms are attributable. Thus, in chyluria with schistosomal disease, there will be chyle in the urine in addition to blood. In such a combination the clot which forms will be larger. will contain oil granules, globules, and very probably microfilaria, in addition to schistosome eggs; moreover, the microfilariæ will generally be detectable in the finger blood if looked for at night. Stone in the bladder, when suspected, has to be

sought with the sound. In gonorrhead cystitis a history of gonorrhead will be forthcoming. In prostatic disease enlargement of the prostate may be made out. Difficulty may sometimes arise when eggs are scanty, or have ceased altogether to come away in consequence of the death of the parent worms. Snips of tissue taken from the bladder or rectum are digested in 10 per cent. potash and examined for eggs (Gelfand and Ross). The mischief wrought by the parasite remains, although the eggs—the most certain evidence of the parasite's previous presence—may no longer be discharged. But, even if the eggs are very few, they may still be found in the last drop or two of urine passed. If they are not found in the urine, sometimes, by scratching the surface of the bladder with a sound and examining the shreds of inucus so obtained, a few, calcified it may be, but presenting the characteristic spine, may be seen with the microscope. Confirmatory evidence may be obtained from the pus cells, the majority of which are eosinophils. By examining urine sediments with the addition of water in a special rack with each tube at 40° to the horizontal, Meeser and colleagues have shown that the hatching miracidia from eggs may be observed with a hand lens. Tubes of urine are spun in a centrifuge at low speed and water is added to correspond with the apertures in the rack, but must not contain any injurious substance. The miracidia stand out shiny and bright against the dull background. Fifteen minutes is allowed for hatching and the number of miracidia varies. An average infection shows 10~20 per tube. Further evidence may be obtained by the tests described below.

Complement-fixation.—Fairley in 1917 described a complement-deviation test employing as antigen an extract of the livers of infected snails (*Planorbis boissyi*). This antigen is prepared by macerating a number of livers containing cercarize of S. mansoni in absolute alcohol, filtering, and evaporating by means



Fig. 142.—Schistosoma hæmatobium eggs in urine, showing contained miracidia. (Dr. H. K. Giffen.)

of a Sprengel's pump. A saline extract is then made of the dried residue and its anti-complementary dose estimated. The general technique is the same as for the quantitative Wassermann reaction in syphilis. Alves and Blair have improved the antigen and avoided false positive reactions by preparing an extract of cercariæ.

The reaction is apparently a group reaction, in so far as an antigen prepared from cercariæ of $S.\ mansoni$ will give positive results with $S.\ hamatobium$ serum in 89 per cent. of early cases; further, Bettencourt and Borges stated that similar reactions take place with $Fasciola\ hepatica$ antigen. A positive result may be obtained in early infections even before the appearance of eggs in the dejecta. It is not so specific in the later as in the earlier stages, but may be employed as a check to treatment.

Intradermal reaction.—Fairley elaborated an intradermal test, similar to the Casoni reaction in hydatid. A saline extract of dried livers, 0.5 per cent., of Planorbis exustus infected with S. spindale of the goat, is used. The extract, having been rendered bacteria-free by passage through a filter, is injected intradermally in a dose of 4 min. A positive reaction is given by an immediate wheal and a zone of erythema with outrunners, and a delayed type of reaction

in from five to eighteen hours. This test is useful as a means of diagnosis in all forms of schistosomiasis, but remains positive for years after the patient has been cured. The results have been improved by using the cercarial antigen of Alves and Blair.¹ The measurement of the wheal is twice the size of the control.

Culbertson and Rose (1944), have obtained a satisfactory antigen from the distome of the frog (*Pneumoneces medioplexus*) which inhabits the lung. The specific fraction is water soluble, and gives reliable intradermal reactions.

Cercurial reaction.—Living schistosome cercariæ, when placed in serum from men and animals recently suffering from schistosomiasis, develop a close-fitting transparent membrane which differs from the loose precipitate which collects around similar cercariæ in normal human or animal serum (Alves). Vogel and Minning describe the same phenomenon as "Cercarial Hüllen reaction" (C.H.R.), and believe that the test may be used as an aid to diagnosis.

Cystoscopic examination.—In the early stages of the localized disease (within two months of infection) the cystoscope reveals sparse grey discrete elevations in the trigone around the ureteric orifices; later, definite hæmorrhagic papules appear with surrounding inflammation. Later still, characteristic "sandy patches," resembling ridges of sea-sand, with papillomata, can be distinguished. (Plate XIX.) These appearances are pathognomonic.

Prognosis.—An important element to be considered, in venturing on a prognosis, is the long life of the parasite. Another important element in prognosis is the degree of infection: the greater the number of parasites, the more severe and the more extensive is the disease they produce. As with filarial infection, the greater the number of cases in a district, the greater the proportionate probability of severe infections. The prognosis is practically that of a chronic cystitis depending on a remediable, and not in itself fatal, cause. Much suffering may often be produced, and, as a consequence, anemia and debility. Possibly calculus may be formed: possibly grave renal disease may ensue; possibly, eventually, villous or epitheliomatous growths in the bladder. In the milder degrees of infection which fortunately are the commonest, the patient seems to be in no way inconvenienced by the parasite, and generally escapes all serious consequences. In any case, mild or severe, there may be attacks of hæmaturia from time to time; as a rule, the quantity of blood thereby lost is insignificant.

TREATMENT

The successful treatment of schistosomiasis by intravenous injection of sodium-antimony tartrate is due to Christopherson. His results have been abundantly confirmed. The drug appears to act upon the adult trematode by cumulative action, and results are judged by observation upon the eggs in the urine. According to Dye, the adult stage of the parasite is most readily affected by tartar emetic; cercariæ and miracidia are less susceptible, while eggs are not affected to anything like the same degree. To test the effect of this drug the freshly-passed urinary deposit is mingled with about sixty times as much warm water at 130° F., and the hatching of the eggs is observed. Under normal conditions this takes place in about five minutes, but after several injections of antimony tartrate they become dark and shrivelled and contain dead miracidia. Christopherson believes this change to be due to the direct action of antimony upon the

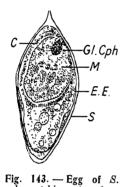
¹ The technique is rather elaborate, and consists of collecting the cercariæ from one infected snail on filter paper, which is subsequently stored in carbol saline in the refrigerator.

eggs (Fig. 144). Fairley, from experimental studies on the allied *S. spindale* of the goat, believes that antimony acts selectively on the reproductive organs of the female schistosome, and thus brings about firstly, the shrunken appearance of the egg and, secondly, cessation of egg-laying capacity.

There is little information about the excretion of antimony compounds used in the treatment of schistosomiasis. Recently, however, Bartler and his colleagues have investigated the excretion of tartar emetic in which radioactive antimony

is incorporated.

Antimony metal was bombarded with deuterons to produce radioactive isotopes. The radioactive antimony was then synthesized into tartar emetic. No untoward effect was produced by the injection during 24 days of a total of 640 mgm. The information so far obtained shows that antimony is excreted more rapidly than formerly supposed.



hænatobium to show de-development of miracidium. S, shell; E.E. embryonic envelope; M, miracidium; C, cilia; Gl. Cph. cephalic glands.



Fig. 144.—Egg of Schistosoma hæmatobium, showing changes produced in contained miracidium by antimony tartrate. (Dr. John Anderson.)

It should be noted that living eggs left in too long contact with alkaline urine fail to hatch; therefore all experiments should be performed with freshly-voided urine.

I. Tartar Emetic (Sodium antimonyl tartrate).—Intravenous injections are given on alternate days over a period of four to six weeks. It is customary to commence with ½ gr. of tartar emetic dissolved in 10 ml. of freshly-distilled sterile water, and gradually to increase the amount by 1/2 gr. until the maximum individual dose of 2-2½ gr. is reached. It is not always necessary to dilute the antimony with 10 ml. of water; for amounts under 1 gr., 6 ml. suffices. Some toxic phenomena may be avoided by dissolving in 5 per cent. glucose solution, but it should not be boiled for any length of time nor subjected to pressure. For large numbers of patients stock solution of tartar emetic is made up in a sterilized vaccine bottle with a rubber cap in a strength of ½ gr. to 1 ml. of distilled water; this can be further diluted later. The solution should be drawn into a syringe of 10 ml. capacity, and slowly injected into the median basilic or cephalic vein. The total amount injected to kill all adult schistosomes is about 25-30 gr. of tartar emetic. Rapid improvement in the condition of the urine should soon be observed; generally all traces of blood disappear after the injection of 15 gr. For children a total of 10 gr. appears to be sufficient, the maximum

individual dose being 1 gr. This course of treatment, once commenced, should be persisted in; cases almost invariably relapse if there are interruptions. In Egypt (1925) the course consisted of twelve injections three times weekly till 22½ gr. of the drug had been administered, and occupied four weeks. When a small amount of diluting fluid is utilized, as suggested, evidences of toxic absorption are noted, such as headache, cough, nausea and transient rheumatic-like pains, especially in shoulder joints, and in the shins.

Fairley confirmed the specific action of tartar emetic on the adult worms. In S. spindale infections of the goat he showed that tartar emetic, in doses of 3.9 to 5.5 mg. per kilo, at daily intervals for a period of from sixteen to twenty-six days, kills the adult parasites and eradicates the disease. Pentavalent compounds of antimony (neostibosan, neostam, etc.) do not seem to be so efficacions

as tartar emetic.

An intensive method of treatment with sodium antimonyl tartrate was introduced by Alves and Blair (1946), with the idea of concentrating the amount of antimony in the shortest period of time, in 100 cases. This method has not been universally successful, and has been subjected to criticism as being too dangerous. The total dosage was 12 mg. per kilo—or 1 gr. to 12 lb. Thus an individual weighing 144 lb. receives 12 gr.

The total dosage is administered in six, seven or eight injections over a period of two days (30 hrs.). When six injections are given they are at 9.0 a.m., 12 noon and 3 p.m. on each of two successive days. Slow and steady injection is essential and should be made at the rate of 2 ml. per minute and a minimum of 5 mins. is taken to complete injection. A fine gauge needle, 23, is used. Ampoules of 1 gr. S.A.T. per ml. of fluid are made up to 10 ml. with 5 per cent. glucose solution. It is claimed that in most cases centrifugalized deposit of the urine on the day after treatment contained no viable eggs and that a large proportion of cases became "skin test negative" within two months. The greater proportion of antimony is excreted by the kidneys, but between 70–80 per cent. remains in the body at the end of 72 hours. The main conclusions have been confirmed by Girges and Aziz, but the method is held to be too drastic for mass treatments.

The intensive method has been recently investigated by Azar and colleagues (1951). They have been unable to discover any evidence of hepatic or renal damage. The E.C.G. changes constitute the only evidence of any toxic effect. These are limited to the T wave which becomes lower and sometimes diphasic or inverted. The avoidance of this treatment in patients with cardio-vascular

disease is self-evident.

Potassium antimonyl tartrate may also be used.

II. Anthiomaline (Lithium antimony thiomalate) is recommended as a more efficacious drug than tartar emetic. There are no contra-indications; intra-muscular injections are not painful, and there is no evidence of either local or general reactions. Anthiomaline is very soluble and contains 16 per cent. of antimony. It is supplied in 2 ml. ampoules of a 6 per cent. solution containing 0.02 grm. of antimony. The initial dose is 0.5 ml. for a child of twelve and 1.5 ml. for others. The maximum individual dose for an adult is 4 ml.; for a child of twelve 2 ml.; and the total dosage is about 65 ml. It is best given by the intravenous route on alternate days.

Mills (1946) has given a synergic course of stibophen and anthiomaline as follows:—the principle was to give a maximum dosage of antimony (0.5 gr.) in less than 14 days. The course of anthiomaline consisted of daily injections of 4 ml. intramuscularly for that period, whilst stibophen was given in 5 ml. doses for five days a week. Those with signs of cystitis were given sulphathiazole 2 grm. daily for seven days. Cystoscopy was performed before treatment, a week after

the last injection and thereafter three times at monthly intervals.

III. Fouadin (Neoantimosan, stibophen).—A trivalent compound containing 13 per cent. of antimony was introduced in 1929 for the treatment of schistosomiasis in Egypt. It is claimed that a cure may be effected in nineteen days, in contradistinction to the more prolonged tartar-emetic treatment. The drug is given intramuscularly in 7 per cent. solution (6·3 per cent. in the latter two preparations) and is put up in ampoules. The dosage is as follows:

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For an adult: 1st day . . . . . . . . 1.5 ml 2nd ,, . . . . . . . . 3.5 ,, 3rd ,, . . . . . . . . . . . . . . 5 ,, Subsequently 5 ml. on alternate days up to the 15th.
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The total number of injections should be from ten to fifteen, totalling 0.4 grm. of antimony. Of this quantity 50 per cent. is excreted in the urine and 4 per cent. in the fæces. Late vomiting occurs in 2.5 per cent. of the cases. There is apparently no local reaction except, occasionally, spasms of coughing. The urine is examined after the last injection, and if living eggs are still present, further injections are indicated. According to Khalil (1930), in 1,474 cases treated with fouadin a cure was obtained in 97.6 per cent. It is, however, generally considered that the results are by no means so satisfactory as by the older method with intravenous tartar emetic.

Orenstein stated that fouadin should never be given intravenously, but should be administered intramuscularly on alternate days. In over 300 school-children treated in this manner no toxic symptoms were observed. Overdosage must be avoided. One of the most serious and permanent injuries is retrobulbar neuritis with central scotoma and loss of colour sense.

Khalil and others have recorded the supervention of post-antimony jaundice in Egypt following mass treatment of the population—about 3 per cent. were affected in 8,000 treated with tartar emetic, whilst there was only one case amongst 2,000 treated by intramuscular foundin. Azar has given foundin in total dosage of 34 ml. of 6·3 per cent. solution over a period of three days and claims better results than with more prolonged treatments.

Trivalent sodium antimony gluconate.—Trivalent SAG (Watson and Pringle, 1950). Burroughs and Wellcome have produced a new compound which can be administered by either intravenous or intramuscular injection. Sterilization by heat is inadvisable. For S. hæmatobium infections it is given intravenously in doses of 180 mgm. daily for six days. The solution is 6 per cent. and the amount injected 3 ml.

Side-effects are notably absent. The total amount of antimony injected is 408 mgm. compared with 566 mgm. in the case of foundin.

V. Emetine.—There is some evidence that emetine is toxic to schistosomes (Diamantis and Erian). The injections should be given intramuscularly to children who are intolerant of antimony, or whose veins are too fine for intravenous injections; generally treatment is commenced with ½-gr. doses, the maximum single dose for a child being 1 gr., while an aggregate total of 15–20 gr. is recommended.

VI. Miracil D (Nilodin) was shown to have definite therapeutic activity by Kikuth and Goennert for mice and monkeys infected with S. mansoni, and by Vogel for animals infected with S. hamatobium. Monkeys tolerate 200 mgm, per kg. four times a week. The first effect is to cause the parasites to retreat from the mesenteric veins. In man it is given by mouth and is readily absorbed in doses of 0.2-0.3 grm. daily. Overdosage produces insomnia, nausea and prostration and sometimes yellow skin discoloration. The great advantage of this compound is that it can be given by the mouth, but, when tested out in African and European schoolboys in Southern Rhodesia, the results were at first doubtful. Now Watson. Abdel Azim and colleagues have obtained better results in Egypt (1948). When higher and more frequent doses were given the results were better. In their most recent series doses up to 300 mgm., at twelve hour intervals, were given as long as fourteen days. In S. hæmatobium infections viable ova disappeared from the urine; in S. mansoni cases eggs vanished from the fæces. The physical condition improved, but most relapsed later. The best results are achieved by keeping the blood miracil D up to the lethal level, by administration every twelve hours.

Alves in Rhodesia has given 10 mgm. per kg. twice daily for three days to a total of 60 mgm. per kg. The drug was given in sugar enteric coated tablets. The cure rate in boys at this dosage was 60.5 per cent. For adults the dose was 100 mgm. per kg. and the cure rate 47.3 per cent. With uncoated tablets absorption is greater and the cure rate higher.

Blair in S. Rhodesia used relatively higher doses of Miracil (up to 25 mgm. per kg. daily in two doses) over a period of five days for children infected with S. hæmatobium. This is more effective than more prolonged dosage compared with the results. S. munsoni is much more resistant.

The following dosage is recommended:

Weight of Patient.	Total Dosage.	3-day Course.	6-day Course.
kg. 20 lbs. 44	1200 mgm.	Daily dose 400 mgm.	Daily dose 200 mgm. ,, ,, 400 mgm. ,, ,, 800 mgm.
,, 40 lbs. 88	2400 mgm.	,, ,, 800 mgm.	
,, 80 lbs. 176	4800 mgm.	,, ,, 1600 mgm.	

TABLE X.—DOSAGE OF ANTIMONY COMPOUNDS

Compound.	Percentage of Antimony.	Total Dosage.	
Ant. potass. tart. Ant. sodii. tart. Stibophen. Fouadin. Anthiomaline.	36 39·5 13·5 13·5 16	1.9 grm. 1.6 grm. 40-75 ml. 60-65 ml. 50-65 ml.	

Local measures.—Stone and troublesome new growths are removed by operation. Mackie and others reported good results from perineal cystotomy and drainage when distress is extreme. Perineal fistula must be dealt with on ordinary surgical principles. Hyperplasia of the vagina and cervix is best treated by scraping. If, by care, re-infection from water can be avoided, there is no need to send the patient away.

Prophylaxis.—Most of the general measures detailed here are applicable to the other forms of human schistosomiasis. They resolve themselves into (1) the protection of snail habitats from fouling and

infections; (2) destruction of snail populations; (3) avoidance of cercarial infection. The first measures are not easily applied, but the advantages are obvious, especially by education and propaganda, which has met with considerable success in the Sudan. The sanitary measures comprise the



Fig. 145.—The intermediary hosts of S. hæmatobium and S. mansoni (Planorbis boissyi and Bulinus contortus) in their natural surroundings. Nat. size. (J. K. Lund, del.)

siting of all villages at least 300 metres from snail-infested canals, which are fenced around, and the provision of good wells and latrines near the villages. These combined with mass treatments have already resulted in substantial reduction in incidence in the Northern Province, in the Wadi Halfa district and in the Blue Nile Province.

The second consists of killing or eliminating the snail intermediaries. These comprise the introduction of chemicals, the removal of snails by manual labour, the removal of aquatic vegetation and other elements necessary for their environment, biological control by introduction, or encouragement, of natural enemies, or unsuitable types of vegetation, reconstruction of natural water-courses, flushing and draining of such water-courses. The chemicals employed are copper sulphate, copper carbonate, ammonium sulphate and slaked lime.

Khalil and Azim used copper sulphate in a concentration of five parts per million for five days in the streams and channels of the Dakhla Oasis with effect. Baugé in Tunisia has confirmed their results. Malachite (basic copper carbonate) has been found in Southern Rhodesia to be as effective and less toxic, but more expensive and less soluble. The system of control in the Fayoum Province of Egypt combines the copper sulphate treatment of the larger canals with manual clearance of snails and the clearing out of vegetation from the smaller water-courses. The concentration of copper sulphate varies from 50 parts per million according to the amount of silt and vegetation present. The application of slaked lime 0.1 per cent. solution kills snails and their eggs in a day; by this method and, in the course of several treatments, canals and tanks have been kept free from them for six months. One treatment every three months usually suffices. Lime has the advantage of being non-toxic to domestic animals and also to cultivated land. The efficacy of drying up the canals, ponds and watercourses, which was advocated originally by Leiper, is doubtful for Bulinus truncatus cannot be exterminated by emptying and drying the canals for 40 days. Even in pools in oases miles removed from the Nile and main channels these snails reappear initiaculously, directly they fill up after rains. Probably the eggs are reintroduced on the feet of ducks and other water birds, but Barlow has shown that the chief species of snails can withstand desiccation for one year at least.

In the endemic districts, children, in particular, should be carefully and repeatedly warned, by school and religious teachers, against drinking or bathing in rivers, ponds, and canals. (Fig. 145.) Sportsmen should be warned against wading, especially when shooting snipe, in localities known to be infected; even fishing in fresh-water canals in countries like Egypt is not free from risk. Swamps, when slightly brackish, are safe. Drinkingwater should be boiled, and every care must be exercised to prevent the diffusion of the disease by prohibiting the evacuation of excreta into or near water, where the miracidia might find the opportunity of development and transmission. This prohibition should not be restricted to patients exhibiting definite symptoms of the disease, but extended to all, because, as special inquiries have shown, a large proportion of the infected do not suffer from any troublesome symptom and are often unaware of their infection.

Khalil states that in 1928 all bulinus snails were completely exterminated in the isolated irrigation region of Wardan in the west of the Nilo Delta, by mixing copper sulphate, 1 in 200,000, in the entering water. A few months later they were present in large numbers, some being found on weeds caught by the pillars on a wooden bridge at the entrance of the canal. It therefore seems as if all the canals in the Delta were restocked from the Nile. That infected snails are

found in the Nile there appears to be little doubt, for 25 per cent. of the children who have never left Roda Island (which lies opposite Cairo) are infected with S. hæmatobium. Biological control by keeping ducks, hedgehogs and fish which feed on the snails has only limited application. Control by aquatic plants—especially by growing the water-hyacinth—Pistia stratiotes—has been suggested as it has been observed that snails are scanty in waters when the surface is covered by them.

A suggestion for practical prophylaxis of schistosomiasis was that of Archibald in the use of the fruit of Balanites agyptiaca, a tree which grows naturally in the irrigated areas of Africa. Prophylactic measures suitable for one area are unsuitable for another, and the Arabs resent chemical treatment of Bulanites ægyptiaca fruits prolifically for six months their only potable water. annually; the date-like fruit is eaten, but the berries, kernels, bark, roots and branches contain an active principle which is deadly to molluses, miracidia, cercariæ, tadpoles, and fish. For actual use the berry is advised: one weighing 5.2 grm. suffices to kill schistosomal molluses when soaked in 30 litres of water. Thirty-five berries are added to a 43-gallon petrol-tin of water and stood overnight. The next morning the softened pulp is crushed in water and stood for twenty-four hours, and this suspension is added to a cubic metre of water. This suspension may be obtained naturally, if there is a dense afforestation of these trees on the borders of canals and pools which harbour schistosome-carrying snails. Ransford in the Kota Kota district of Nyasaland has shown that the leaves of a shrub—Tephrosia vogelii—which is easily cultivated—acts as an efficient molluscicide in a strength of 1:4,000. It is commonly used by the native population as a fish poison, but is harmless to human beings and animals.

The third measure—avoidance of cercarial infection—is more practical. It consists of avoidance of skin contact with or drinking of infected water. It has been shown experimentally that cercariæ only penetrate the skin when water is evaporating—hence vigorous wiping with a towel after bathing is a useful method of prophylaxis. Cercaricidal substances are employed. Originally Witenberg and Gofe found chloramine more effective than gaseous chlorine or sodium hypochlorite. The concentration necessary is 0.22 parts per million residual after tenminutes' application for chloramine, 0.42 for sodium hypochlorite and 0.6 for gaseous chlorine. The heat of the direct rays of the sun is lethal to cercariæ.

DDT has been found to possess slight anticercarial action.

It has been noted in pools in S. Africa which had been sprayed with DDT from the air that there is a rise in the snail population, and therefore increases the chance of infection with schistosomes. In a search for potent molluscides von Brand and his associates have found only two of any value—pentabromophenol and pentachlorophenol—but both are extreme irritants to the mucous membrane of the respiratory tract.

Mass treatments.—The efficacy of prevention in any anti-schistosomal scheme is

greatly enhanced by concurrent treatment of the infected population.

II. Intestinal Schistosomiasis (Schistosoma mansoni) Synonym.—Intestinal bilharziasis; Schistosomal dysentery.

Definition.—A chronic endemic disease caused by *Schistosoma* mansoni, giving rise to dysenteric and other symptoms referable to the intestinal canal, is characterized by appearance of lateral-spined eggs in the fæces. In the early stages there may be general symptoms, such as fever and urticaria, indicating absorption of the toxins excreted by the parasites. One of the visceral manifestations of this infection is Egyptian splenomegaly, a common disease in Egypt and Northern Nyasaland, in many respects resembling kala-azar.

Epidemiology and geographical distribution.—Schistosoma mansoni requires slightly different conditions for its propagation from those of S. hæmatobium, so that, though frequently found associated in Africa, yet there are areas in the Southern Sudan and in West Africa where S. mansoni is prevalent and S. hæmatobium absent. Although schistosomiasis occurs in eleven out of fourteen provinces in the Sudan, S. hæmatobium is the common type in the north, and south of the Upper Nile Province S. mansoni alone is found. (Map VII.)

Infection is acquired during the months of the year when water is sufficiently shallow to permit a high concentration of cercariæ. In inland lakes the seasonal incidence is from October to the end of January, but in the Nile backwaters the danger period is usually February to June.

In South America, especially in Surinam and Venezuela, S. mansoni is widespread; in the latter country it forms an important problem, and 30,000 are infected in one area, the central part of the Northern coastal range where the intermediary, Australorbis glabratus, is found. Infestation is commonest where sugar cane is irrigated. In several communities at least one quarter are infected, especially men. Whenever snails occur near houses the women are as highly infected as men, and the children acquire infestation early. The West African green monkey (Cercopithecus

sabæus) constitutes a reservoir of S. mansoni infection in W. Africa, and also in St. Kitts in the Lesser Antilles where it now lives in a feral state.

Ætiology.—The parasite much resembles S. hæmatobium. The distinguishing features are that it is generally smaller and more grossly tuberculated. There are other points (Fig. 146). The female deposits one or two eggs at a time—a circumstance perhaps explicable by the peculiar structure of the uterus. The eggs are somewhat spindle-shaped, provided with a lateral spine (Plate XXVI, 12, facing p. 1079) and are generally slightly shorter than those of S. hæmatobium, 0·15 mm. in length by 0·06 mm. in diameter. These eggs are passed out in the fæces, rarely in the urine, and hatch out a ciliated miracidium. (See also p. 710.) This species may live in man for 26 years.

Pathology of intestinal schistosomiasis.— The eggs of S. mansoni may be found in great numbers in the liver, where they give rise to a peculiar form of "pipe-stem" cirrhosis. Sandy patches, due to effete calcified eggs, cover large areas of the intestinal surface, and may give rise Black pigment granules are deposited in the inter-

to acute choleraic diarrheea. Black pigment granules are deposited in the interstitial and secreting cells of the liver, and have been shown in both S. mansoni and S. hæmatobium infections, but are commoner and more abundant in the former.

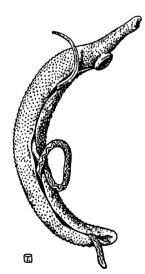


Fig. 146.—Schistosoma mansoni, male and female × 6. (After Looss.)

¹ Formerly Planorbis guadeloupensis.

It is golden brown or sepia, and gives the same reactions as malarial pigment (hæmatin). The gall bladder has very rarely been found infected. The lymph-glands in the retro-peritoneal tissue are enlarged. There is generally an appreciable hypertrophy of the spleen, which may possibly be attributed to toxic absorption and which gives rise to the clinical syndrome known as Egyptian splenomegaly.

The affections of the colon may be classified into four types—(a) those with simple thickening of the mucous membrane; (b) thickening of the mucosa with papillomata and ulcers; (c) pericolic tumours associated with papillomata; (d) polypi of the execum which may lead to intussusception. Infiltration of the appendix with S. mansoni eggs is not uncommon and may give rise to the signs and symptoms of acute appendicitis, which is complicated by secondary bacterial infection.

The small intestine is hardly ever affected, except in its lower part. In the colon the disease causes the formation of septic foci, and ulceration of the bowel-wall appears to be produced by the tearing-off of pedunculated papillomata by the peristaltic action of the intestine. By this means, and by sloughing at the base, are produced clear-cut ulcers which may become subsequently infected with *Entamæba histolytica*. Perforation of the bowel may occur. Fairley and Lampe drew attention to the similarity of the disseminated pericolic nodules to miliary tuberculosis and also to infiltration of the mesenteric glands by schistosome eggs. Disseminated bilharzial tumours of the peritoneum closely resemble carcinomatosis (Trim).

Shaw and Ghareeb emphasized the importance of pulmonary damage as the cause of death in *S. mansoni* as well as in *S. hamatobium* infections. The main damage is due to embolism by eggs derived from female flukes outside the lung. They are filtered out in the arterioles which accompany the bronchioles, producing diffuse arterial changes resembling Ayerza's disease. Parenchymatous tubercles are found containing the characteristic eggs. In some 10 per cent. of cases, the adult worms have been found in the pulmonary veins.

VISCERAL SCHISTOSOMIASIS; HEPATO-LIENAL FIBROSIS; EGYPTIAN SPLENOMEGALY

Splenomegaly, associated with cirrhosis of the liver, is common in all parts of Upper and Lower Egypt, where 20 per cent. of infants under four years of age are found to have splenic enlargement and anæmia. It is common among the working class at all ages up to thirty; in the young it is apt to run a severe course, while at a later age the chronic form, progressing to ascites, is met. In children the disease is generally associated with rickets, in adults with ancylostomiasis. A similar syndrome was recorded by Dye from Northern Nyasaland in patients also infected with Schistosoma mansoni. Originally, Day came to the conclusion that in Egypt this disease is a peculiar manifestation of S. mansoni infection. He regarded it as distinct from Banti's disease in that the hepatic changes are noted from the commencement, while the eosinophilia and recurrent fever disappear under specific treatment with tartar emetic. Hyperplasia of the spleen appears to be secondary to hepatic cirrhosis, and to this condition are to be ascribed the anæmia and leucopenia which are found in advanced cases. Those with advanced cirrhosis are just those who have few intestinal symptoms, and who pass scanty, or, it may be, no eggs in the stools. To account for this anomaly it has been suggested that in these cases unisexual infestation with a preponderance of male worms exists. Eggs of S. mansoni may be found on digestion of solid organs, such as the liver and spleen, with potash. This form of schistosomiasis does not appear to be found in South America, but has been reported from N. Africa in association with S. hæmatobium (Blanc and Touzin).

Pathology of hepato-lienal form (Egyptian splenomegaly).—Ferguson recorded that the average weight of the spleen is 30 oz.; it may reach 300 oz., and, according to Day, may contain scanty eggs of *S. mansoni*. It is firm; microscopically there is a general hyperplasia with active phagocytosis of red cells by macrophages.

Onsy stated that the only certain method of finding eggs in these spleens is by maccrating the tissues in 20 per cent. soda solution and then centrifugalizing. The eggs are phagocytosed by giant cells, a process accompanied by considerable eosinophilia. In order to account for the widespread nature of the visceral lesions and the paucity of eggs, the view was put forward by Girges and others that, Egyptian splenomegaly is caused by infection by male Schistosoma manson, in the absence of the female; but this view is not widely held. On the other hand the presence of "spinster" females has been reported.

Abdel Shafi claimed that, although the incidence of eggs in the liver is fairly high, yet other organs and tissues show much heavier deposits, that infection of the liver alone is unknown, and that the number of eggs in the liver substance is small in comparison with the extensive cirrhotic changes in that organ.

The liver is usually enlarged in the early stages, and presents the picture of early multilobular cirrhosis with isolated necrotic foci. In the more advanced stages the organ is shrunken and firmly fixed to the diaphragm by adhesions. There is a comparative absence of bile-duct formation. The bone-marrow shows no great disturbance of the hamopoïetic system.

Symptoms of intestinal schistosomiasis.—As in S. hæmatobium infections, the earliest manifestations are associated with the entry of the cercariæ into the skin, and consist of an irritative dermatitis depending



Fig. 147.—Rectal schistosomiasis adenomata prolapsed through anus. (After Madden.)

upon the intensity of exposure. Within a few hours minute petechiæ may be observed at the sites of invasion of blood vessels, but these disappear in a day or two.

S. mansoni inhabits chiefly the branches of the portal vein in the liver and the mesenteric veins. Its eggs, deposited within the submucous layer of the large intestine, give rise to dysentery-like symptoms, commencing six to eight weeks after infection; mucus with blood is passed from time to time, the egg-laden stools becoming frequent and their passage being perhaps attended with tenesmus. In certain well-established cases small (sometimes large) branching, soft growths are felt inside the sphincter ani. (Fig. 147.) They resemble

polypoid growths and are apt to be mistaken for internal piles. They may extend as high up the bowel as the sigmoid flexure. If one of these

growths is teased up, the lateral-spined eggs are seen in the debris.

In heavy infections, in early cases, toxic symptoms resembling those of katavama disease (p. 729) are noted, especially in Europeans. General symptoms consist of intermittent pyrexia, with giant urticaria, abdominal pain, anorexia, rigors, and pulmonary symptoms. (Chart 27.) The very evident urticaria, often accompanied by swelling of the face and lips, is thought by some to be due to destruction of cercariæ in the skin capillaries; by others to the filtering out of foreign proteins from the portal circulation. Pons stated that cough is invariably present in early cases, and tenderness is found over the liver, spleen, and intestines, especially over the cæcum. On abdominal examination of dysenteriform cases enlargement of liver as well as of spleen is frequently found. A pronounced leucocytosis with high eosinophilia (up to 76 per cent.) is invariable.

Later, localized symptoms, with passage of

dysenteric motions, supervene.

In the terminal stages large palpable abdominal tumours may form, and intestinal stasis or distension may take place. Infiltration of the buttocks with eggs, leading to induration and fistulæ, is not uncommon. When the liver has become markedly cirrhotic, ascites may be present. Pneumonia from egg-deposition in the lungs is an occasional complication¹.

Sometimes dysenteric attacks may develop into acute diarrhæa, of choleraic type, which may prove fatal. Deposition of the eggs in the appendix occurs comparatively often and produces symptoms of a subacute appendicitis. Generally, the organ is much thickened and infiltrated so that it can easily be palpated. The diagnosis of schistosomal appendicitis from septic or amæbic appendicitis may be difficult. Chronic intestinal obstruction may result from schistosomal tumours and may be accompanied by serous peritonitis (Trim).

¥ £ Ĕ Chart 27.—Four-hourly temperature chart of acute schistosomiasis (S. munsoni). (Lawton. Ĭ ٤ Ĕ Ĭ 돌 Ĕ 통 £ 튭 Ĕ ٤ É Ĕ ŧ Pm 2 6 to 6 10 £ 26102 Ĕ £ 9 20 ₫ 8

Symptoms of the hepato-lienal form (Egyptian splenomegaly).—The symptoms

of this condition,

¹Pulmonary sclerosis resembling Ayerza's disease appears to be comparatively common (Erfan, 1948).

commonly known as "Egyptian splenomegaly," appear to be more objective than subjective. There are irregular fever, wasting, and a striking pallor. The spleen is obviously enlarged, hard and firm, often reaching to the umbilicus (Fig. 148); the liver also in the early stages is enlarged. Vomiting and diarrhœa are frequent. In the later stages œdemas, of varying degree, and purpuric rashes may ensue. The fever is generally irregular, intermittent, and not amenable to quinine or other antimalarials. The splenic enlargement causes pain and discomfort, especially after meals, and on exertion gives rise to a dragging sensation, though the main symptoms are caused by debility and anamia. As the disease progresses, so pyrexia increases, until the steady enlargement of the liver and spleen causes the costal angle to expand. Hæmatemesis often occurs, but jaundice is rare. Hepatic abscess associated with visceral



Fig. 148. — Egyptian splenomegaly. (Dr. S. C. Jones.)

schistosomiasis has been reported by Graham. The final stage is ushered in by cirrhotic changes in the liver, which becomes hard and firm and shrinks within the costal margin. The spleen also becomes fibrotic, but does not proportionately decrease in size. The pain, which is due to perisplenitis and perihepatic adhesions, increases, while vomiting is common. Finally, the patient succumbs with symptoms of hepatic cirrhosis, ascites, and emaciation. Death is usually due to pulmonary complications.

Kenawy described a continuous venous hum which may be heard by the stethoscope over the liver, and which he considers is characteristic. The hum becomes louder during inspiration, and also in the erect position. After splenectomy the sound disappears; this is probably due to the removal of some venous communication. Unfortunately, this sign is of no great assistance in differential diagnosis, for a similar hum has been noted in other forms of cirrhosis, as well as in Banti's disease.

The blood picture varies. In the early stages there is a leucocytosis

of 17,000 and myelocytes may be present; later, progressive anemia of the microcytic type becomes apparent, with leucopenia of 3,000 and a mononuclear increase of 10-17 per cent.

Among the rarer complications, thrombosis of the portal vein and hepatic carcinoma have been recorded.

The course of the disease is generally protracted: in older children and

adults it may run twenty years or more. Ascites is always regarded as unfavourable. In all its aspects this stage resembles that of schistosomiasis japonica.

Diagnosis.—The characteristic eggs are easily found in the fæces under low powers of the microscope; they may be very scanty, and it is necessary to examine three or more specimens before arriving at a negative diagnosis. (Fig. 149.) They are more easily found in solid than in fluid stools, especially in the outer portions of a motion. Quite a high proportion of cases are latent—that is to say, they do not present any recognizable or urgent symptoms. The Editor found examination of mucus and scrapings from the rectal mucosa, obtained through the



Fig. 149.—Microphotograph of miracidium of Schistosoma mansoni escaping from egg. × 1,500. (Dr. A. J. Chalmers.)

proctoscope or sigmoidoscope, more reliable than fæces examination. Crypt-aspiration by special suction apparatus has been practised by American specialists. Allen Scott also considered that the highest diagnostic efficiency is obtained by rectal swabs. On examination of over 1,000 fæcal specimens by three different techniques and by a combination of them—viz., egg-counting by Stoll-Hausheer method, using 0.005 ml. of fæces diluted in decinormal soda, sedimentation in normal saline consisting of concentrated egg-count and swabs—he found that the latter method gave the best results. In about 5 per cent. of cases in Egypt the characteristic eggs may be found in the urine as well as in the fæces.

Fülleborn recommended the Telemann method of finding the eggs when scanty. The fæces are shaken up with a mixture of concentrated hydrochloric acid, l part, water, l part, ether, 2 parts, and strained through gauze; the filtrate is centrifuged and examined. The deposit may then be mixed with water and the eggs encouraged to hatch, when the miracidia are more easily detected (Appendix, p. 1084).

In this form of schistosomiasis the total serum proteins do not vary much from normal, but the globulin and globulin-albumin rates and the percentage of euglobulin are increased, more especially in patients with splenomegaly (Khalil and Hassan). The formaldehyde test may, therefore, constitute a reliable means of differentiation from leishmaniasis.

The complement-fixation and intradermal tests are the same as in S. hamatobium infections (p. 711). Pifano and Mayer have recorded good results in Venezuela with alcoholic extracts of the hepato-pancreas of infected Australorbis glabratus; more recently with extracts made from adult S. mansoni which give 95 per cent. of positive reactions. In the stage of invasion antibodies appear at the beginning of the third week. Standen has devised a special technique for concentrating cercariæ of S. mansoni for the preparation of antigen.

In rectal disease, should S. mansoni be suspected, an adenomatous

growth may be removed by forceps and examined for eggs. .

Sigmoidoscopic examination usually reveals pedunculated adenopapilomata in the upper part of the rectum, but usually this is unnecessary, as they can be felt by digital examination and may sometimes be seen protruding in polypoid masses from the anus. In very early cases granular patches can be detected on the rectal mucosa from which eggs may be obtained by scraping with a blunt Volkmann spoon through the sigmoidoscope or proctoscope. The localized thickenings of the large intestine, due to polypi and pericolic growths in the transverse and pelvic colons, may be palpated in heavily infected subjects.

Differential diagnosis of the hepato-lienal form has to be made from splenic anemia and other forms of splenomegaly. It is stated that injections of adrenalin decrease the size of the spleni in splenic anemia, but are

without effect in schistosomiasis.

TREATMENT

I. Antimony treatment.—Gross changes in the organs are more extensive than in S. hæmatobium infections, due partly to toxic absorption and partly to deposition of eggs, and it is possible, as Madden and Day asserted, for adult trematodes to be extirpated by tartar emetic without affecting the fibrotic changes. Hence, it may prove necessary to remove polypoid or adenomatous growths obstructing the intestines. In early cases antimony is as successful as it is in S. hæmatobium infections. Lampe in Surinam treated out-patients with three injections of 3 ml., 5 ml. and 7.5 ml. of a 1 per cent. solution of tartar emetic thrice weekly—a total of 150–200 ml.—the whole course occupying six to seven weeks. Dye and others gave rectal injections of tartar emetic as being especially suitable for children, who can tolerate 16 gr. by the rectum without toxic effects, but the amount of the drug absorbed is unknown. Five to seven daily intrarectal injections are necessary.

S. mansoni is more difficult to exterminate than S. hæmatobium, and requires larger doses of intravenous tartar emetic—up to a total of 50 gr. As in S. hæmatobium infections, fouadin has been extensively employed as an intramuscular injection, especially in Egypt, but it does not appear to be as efficacious as intravenous tartar emetic, while Khalil has reported a few cases of sudden death. From Egyptian statistics in 1934, it is learned that the total number of schistosome cases which received nine or more injections of fouadin was 1,938; of these 53 per cent. were cured, but 21 per cent. required eleven injections, and the remainder even more. After thirteen injections, signs of intolerance were noted. (See p. 715.)

Khalil thought that there are individual variations in the excretion of foundin, and that idiosyncrasies to this drug may occur. The rate of renal excretion is important, and the drug is most easily tolerated by children. Any degree of kidney damage is a contra-indication. Usually, after the fifth injection dead eggs of S. mansoni may be found in the fæces. Relapses are recorded in 33 per cent. of cases. Foundin gives a positive catechol test in the urine—a green colour with ferric trichloride which changes to violet on adding sodium carbonate. If the urine is not clear, it must be centrifuged. Anthiomaline, as in S. hæmatobium infections, is being extensively employed with success (p. 714).

Goodwin (1944) found trivalent sodium antimonyl tartrate to be half as toxic as sodium antimony tartrate. The total course for an adult is up to 16 grm. in daily injections for 12 days.

II. Miracil D (Nilodin) (see p. 716) is given in the same manner as for S. hæmatobium, but this parasite is more resistant. Larger doses are necessary and the treatment must be more prolonged.

Some two thousand Africans in the Belgian Congo with S. mansoni infection have been treated orally with Miracil D. The dosage for adults was 7.2 grm. given in divided doses twice daily for six days amounting to 130 mgm. per kg.

- III. Operative treatment of intestinal schistosomiasis.—Dolbey and Fahmy held that the rational method of obtaining a permanent cure in cases with extensive disease of the rectum is excision of the whole tube of mucous membrane. Lengths of 12–15 in. can be removed with ease. A circular incision is made at the junction of skin and anal mucous membrane; the external sphincter and levator ani attachment are separated by blunt dissection; when once the latter has been separated, the mucous tube may be loosened by the gloved finger and withdrawn until the upper limit of the papillomata is reached. Recovery is uneventful; there is little tendency to retraction of the tube, and control of the anal sphincter is regained. This operation is unsuitable for very anæmic or debilitated patients.
- IV. Operative treatment of the hepato-lienal form.—According to Richards, palliative operative interferences, such as frequent tapping and the Talma-Morrison operation (omentopexy), are permissible in cases with ascites, though in early cases before the development of ascites, he performed splenectomy with success. Coleman, Bateman and Stiven confirmed the value of this operation. The mortality-rate is about 15 per cent. and deaths are due to late shock. Great care is still necessary in the

selection and preparation of cases for operation. Ascites, pellagra, heart disease and debility are contra-indications. Considerable leucocytosis differentiates this condition from leukæmia. In his account of 390 cases, Stiven stated that five to six weeks' preliminary treatment is necessary; it should consist of tetrachlor-ethylene, to get rid of intestinal parasites, and intravenous injections of neosalvarsan for syphilis. The weight of the spleons removed by this surgeon averaged $3\frac{3}{4}$ lb. The favourable results appear to be permanent, and ascites does not develop. Day claimed that early cases are curable with tartar emetic.

Stiven operated with stovaine spinal anæsthesia, making an incision, varying in length with the size of the spleen, down the centre of the left rectus parallel with the middle line, and starting at the costal margin. Skin and rectal sheath are divided by the knife, the rectus muscle being separated into two equal parts by a sweeping action of the finger. The peritoneum being opened, the spleen can be delivered, in the absence of adhesions, through the wound. The pedicle is clamped and the organ removed. The former is now transfixed with a long pedicle needle, armed with black and white linen thread, linen being less apt to slip than silk, and the difference in colour ensuring recognition of the necessary interlocking. After operation, patients are given nothing to drink for twelve hours and then strict diet for five days, and subsequently a purge. Nourishing diet and iron and arsenic are necessary. Patients usually leave hospital after fifteen days.

Observations made in Egypt upon the late results of splenectomy have been summarized by Abdou and Grace. Of 35 operated during a period of ten years 30 were alive. Of the five fatal cases, one died of portal thrombosis. The general results were considered good. The lassitude and anæmia disappeared; nutrition was restored and health maintained. In Pernambuco, Brazil, da Silva operated upon some sixty during 6½ years. Maximum incidence was between 15–24 years. Hæmatemesis due to rupture of æsophageal veins occurred in 56.6 per cent., and this constitutes an indication for operation. Pre-operative antimony treatment is not advised. There were 15 post-operative deaths.

Immunity.—Vogel investigating serological and immunological aspects found that a slowly built-up immunity takes place in both S. mansoni and S. japonicum infections. He exposed rhesus monkeys at monthly intervals to infection with 25 cerearize each. Under these conditions the number of eggs exereted by these monkeys at first increased steadily, but after 6-9 months it began to fall, in spite of superinfection. Finally the egg output ceased almost completely and at this time exposure of the monkeys to doses of cerearize, which would have proved fatal in uninfected monkeys, was with effect. At autopsy live stanted adult schistosomes of both sexes were present.

Prognosis.—This is the same as for *S. hæmatolvium*, but it must be remembered that this disease is generally latent, and that even large intestinal polypi may give rise to little or no inconvenience.

Cases with papillomata of the rectum, dysenteric symptoms, tenesmus, and anæmia, and those with actual obstruction of the intestinal canal and cirrhotic changes in the liver, must be regarded as serious.

Prophylaxis is the same as in S. hæmatobium (p. 716). There appears to be a greater probability of contracting the disease in the neighbourhood of canals and waterways, which are the favourite haunt of Planorbis boissyi, of which a high proportion (50 per cent. or more in some cases) are found to be infected with the cercariæ of this trematode in Egypt. In Northern Nigeria and in Kenya, infection has been recorded from bathing in clear pools in the absence of any obvious aquatic vegetation. In South America and Venezuela prophylaxis is concerned mainly with avoiding collections of water and cane-field irrigation canals which form the haunts of Australorbis glabratus.

In Pernambuco (Brazil), slaked lime has been found most effective against A. glabratus and Biomphalaria (Planorbis) centimetralis. Chlorination of 0.2 parts per million kill cercariæ of S. mansoni in 30 minutes. Krakower found the normal span of these cercariæ in rainwater was 24–48 hours; at 5–6°C. they survive up to 14 days, but remain motionless, but above 34°C. the mortality increases, and at 45°C. all die in 30 minutes. Strong electric light induces activity and shortens lifespan, whilst ultra-violet and direct sunlight are both fatal. Extremes of pH outside the 4·6–10 range are fatal and cercariæ are rapidly killed in a 1·5 per cent. sodium chloride solution.

Berry and others have found eleven chemical compounds effective in killing A. glabratus in high dilutions under natural conditions in Puerto Rico. Six proved effective molluscicides. Sodium pentachlorophenate and copper pentachlorophenate are excellent and their cost reasonable. At 9.5 ppm. calculated at a 6-hour flow-rate destroyed all snails for a distance of 1.5 miles downstream.

III. EASTERN SCHISTOSOMIASIS (Schistosoma japonicum)

Synonym.—Katayama Disease. Bilharziasis japonica.

Definition.—A chronic endemic disease of Eastern Asiatic countries caused by *Schistosoma japonicum*, and characterized by great enlargement of the liver and spleen and ascites. The eggs of the parasite are discharged in the fæces. Initial toxic symptoms, urticaria and pyrexia, are common.

Geographical distribution.—For very many years an endemic disease characterized by splenomegaly, enlargement of the liver, cachexia, ascites, pyrexia, and dysenteric symptoms had been observed in Japan. In 1888 Majima found eggs in a cirrhotic liver, and in 1904 Katsurada saw a miracidium emerge from similar eggs which he had found in fæces; later, he discovered the adult trematode, S. japonicum, in the portal veins of the cat. In that year also Catto found similar parasites in a Chinaman in Singapore. The next addition to knowledge was made by Katsurada, who succeeded in communicating the parasite to cats by immersing their legs in the water of certain ponds reputed to convey the disease. In 1913 Miyairi and Suzuki traced the parasite, through snails common in the infected districts, back to the vertebrate host, a discovery confirmed in the following year by Leiper and Atkinson.

So far, the parasite had been found principally in Chinese and Japanese, though a few Europeans—mostly naval officers and sportsmen, addicted to snipe-shooting in the rice-fields—had acquired the disease. Its present range, as far as is known, may be stated as follows: In China it occurs in endemic foci in the Yangtse basin on both banks from Ichang, 350 miles above Hankow, to the sea; in the provinces of Hunan (Siang River), Hupeh, Anhwei, Kiangsu

and Kiangsi. An endemic centre has recently been reported from Shiuchow, on the North River near Canton, and also from Foochow (Fukien). It has been recorded on the Burmese border between Yunnan and the Northern Shan States. In Japan it is especially prevalent in the province of Hiroshima and in the village of Katayama. Five schistosomiasis endemic areas are known in Japan. The most important extends along the Tone river to N. and E. of Tokio, an extensive rice-growing area. Endemic foci also exist in Southern Formosa, and in the Southern Philippine Islands—Samar, Leyte, Mindanao and in Celebes (Indonesia). Several hundred cases were discovered in American troops within a limited period in October, 1944, during the invasion of Leyte. (Map VII.) In countries where it exists, pigs, dogs, cats, rats, buffaloes and imported cattle and horses are found naturally infected: native cows, on the other hand, appear to be immune.

Ætiology.—The parasite closely resembles S. hæmatobium, though it is smaller and the integument is smooth and non-tuberculated. In proportion, the acetabulum or ventral sucker is longer and stouter than in either S. hæmatobium or S. mansoni. The eggs, smooth and slightly oval, measure 0.08 mm. by 0.06 mm., and pass through the intestines into the fæces. They possess a rudimentary lateral spine, and show considerable variation in size, but in the uterus of the female schistosome they are much smaller than those in the fæces. (See p. 952.) Vogel (1942) has shown that the egg passes through three stages—immature, mature, and degenerate. New laid eggs require 10 days to develop to maturity, The miracidium can live the same period within the egg. In man this parasite can live from 20–25 years.

The miracidium, after casting its cilia, develops in fresh-water molluses of the genus Oncomelania¹, Gredler, 1881, which have a widespread distribution in Japan and China; probably all species of this genus are potential carriers of S. japonicum.

Pathology.—The outstanding feature is the great enlargement of the liver and spleen. The former is hypertrophied and nodular, due to the formation and contraction of fibrous tissue; on digesting with 3 per cent. potash solution, it is found to contain many eggs. The great enlargement of the spleen, on the other hand, is probably due to absorption of toxins or, possibly, to backpressure, as eggs are seldom found there. As in other forms of schistosomiasis, granules of black pigment are found in both viscera. The appendices epiploice are greatly thickened and may be matted together; the mesenteric and retroperitoneal lymph-glands are enlarged; hypertrophy and thickening of the lower parts of the intestinal tract, with formation of ulcers and polypoid growths filled with eggs, are generally noted. The bladder is unaffected.

Occasionally, indurations of the pia mater and granulomatous lesions of the cerebral cortex have been found, eggs being present in great numbers. The young forms of the parasite enter the general circulation through the veins and collect in the lungs, apparently entering the liver by traversing the mediastinum and the diaphragm. Inside the portal system they soon reach maturity. Infection of the fœtus during intra-uterine life is apparently possible.

Symptoms.—The disease produced by S. japonicum is serious and, when pronounced, sooner or later proves fatal. The gravity of any given case depends, amongst other things, on the degree of infection and the circumstances of the patient. Of 1,077 persons near Shushima, Japan, examined by Koiki, 42 were found infected. Of these, only 22 were not in good health. Penetration of the skin by the cercariæ causes an intense

¹ There has been much confusion about the correct nomenclature of these snails; the reader is referred to Appendix, p. 954.

pruritus, partly mechanical, and partly due to an irritating substance secreted by the larvæ. The erythema thus produced was formerly regarded by the Japanese as a skin disease, "kabure," and is similar to that of the two other forms of schistosomiasis.

The course of the disease can be divided into three stages: invasion. deposition and fibrosis. The first (Katayama disease) occurs shortly after infection and lasts about a month. It is associated with toxic symptoms -pyrexia, giant urticaria, abdominal pain, paroxysmal cough, leucocytosis, and a high eosinophilia (60 per cent. more). Dermatographia and angioneurotic œdema are common. As in the case of S. hæmatobium, eggs have been found in multiple skin lesions by Fishbon (1946) in American soldiers in Levte. The lesions consisted of pruritic papules in chest and scrotum. Biopsies showed inflammatory reaction with eosinophile cells surrounding distorted schistosome ova. Garcia found eggs in biopsy of chronic ulcer on the leg of a child The second is characterized by great emaciation and is accompanied by dysenteric symptoms and enlargement of liver and spleen. Abdominal pain in right hypochondrium is severe. The third or final stage, when it does supervene, occurs from three to five years after infection. In this the liver and spleen are cirrhotic and enlarged (hepato-lienal Ascites and cedema of the fibrosis). extremities appear, with anæmia and exacerbations of dysenteric symptoms (Fig. 150). The patient may die of exhaustion, of some terminal infection, or of Jacksonian fits or hemiplegia. S. japonicum eggs tend to be localized in the brain and C.N.S. Total blindness, owing to deposition of eggs in the cerebral cortex, or destruction of the visual centres may ensue.



Fig. 150.—Terminal stages of Eastern schistosomiasis. (Photograph by Dr. J. A. Thomson; by courtesy of Wellcome Bur. Sci. Res.)

Faust and Wright, reporting on the outbreak amongst American troops in Leyte in early cases, recognized a fulminating type, a severe

type with sudden onset, an insidious type and quite numerous asymptomatic cases. In the severe forms a relatively common symptom was "nuchal rigidity." A complication supervening in the chronic form is cæco-colic intussusception. The ileum may be invaginated into the ascending colon. In light infections the only constant sign is a tender palpable liver (Johnson and Berry). Marked leucocytosis and eosinophilia are associated with the first two stages.

Diagnosis.—All cases of urticarial fever from the endemic districts should be watched for many months (especially if eosinophilia persists after the subsidence of the primary attack) and the stools examined for eggs of S. japonicum. All cases of chronic intestinal disturbance from the districts mentioned, especially if associated with enlargement of liver and spleen, should be regarded as possible cases of schistosomiasis, and the blood and stools should be examined. If the characteristic eggs (Fig. 151) are discovered definite diagnosis is established. Fæces concentration methods for demonstration of eggs are frequently necessary.

Complement-fixation reactions and intradermal tests, as in S. hæmatobium



Fig. 151.—Eggs of S. japonicum in fæces. × 250. (Microphotograph by Dr. J. Bell.)

infection, can be carried out with antigen made from corcariæ of S. spindale of the Indian water buffalo. Williams has shown that the antigen remains effective in sealed ampoules for eighteen years. A similar reaction is obtained with extracts from the bodies of the adult trematodes when the serum of artificially-infected horses is used (Seuzasu, 1917). Most has employed intradermal tests with antigens made from adult schistosomes and found them specific. Pesigan (1950), using cercarial antigen prepared by method of Alves and Blair, concluded that the resulting wheal should be measured at intervals of 5, 10, 20, and 30 minutes after intradermal injection. According to Faust and Meleney, the aldehyde or serum-globulin test is strongly positive in many cases.

It is said that ferments are given off by the adult schistosomes, one of which is allied to trypsin and digests albumin in an alkaline medium.

The disease in its terminal stage has to be differentiated from Banti's disease and from kala-azar. Campbell states that most cases diagnosed as Banti's disease in the Far East are in fact schistosomiasis japonica. Louchs suggested that a safe method of making a positive diagnosis is by biopsy of the liver during splenectomy, and the demonstration of the eggs, when they are not apparent in the fæces. Sigmoidoscopy as in S. mansoni is of value. In early cases yellowish nodules are seen on the mucosal surface of the lower sigmoid and upper rectum. These are elevated papules 1-3 mm. in diameter which on scraping yield eggs of S. japonicum (Faust). Rectal biopsy and crypt aspiration are of value to demonstrate eggs (Hollands and Palmer, 1946). Pathognomonic losions are seen in 67 per cent. of cases. The method consists of a heavy-walled bent-tipped glass pipette connected with a motor-driven suction pump, developing 20 in. mercury vacuum. Suspicious lesions are scraped and aspirated.

Differential diagnosis has to be made also from Jacksonian epilepsy, cysticercosis and tumours of the brain, since deposition of *S. japonicum* eggs in the cerebral cortex may give rise to granulomata of considerable size.

Treatment.—Antimony tartrate, given in the same doses and in the same manner as for S. hæmatobium, appears to be efficacious in killing adult trematodes. A total amount of 24 gr. or more is necessary. According to Faust and Meleney, 20–30 gr. of intravenous tartar emetic over a period of eighteen to twenty days is usually curative. Anthiomaline is probably better than tartar emetic. The Americans in Leyte found the pentavalent compounds of antimony ineffectual. Kastein and others claimed that intramuscular injections of fouadin in doses up to 5 ml. are effective, as in S. hæmatobium infections, but the full course, as detailed on p. 715, must be given. At least 16 injections are necessary. Pesigan in extensive trials gave up to 40 ml., and in many instances more than one course had to be given—up to 65 ml.

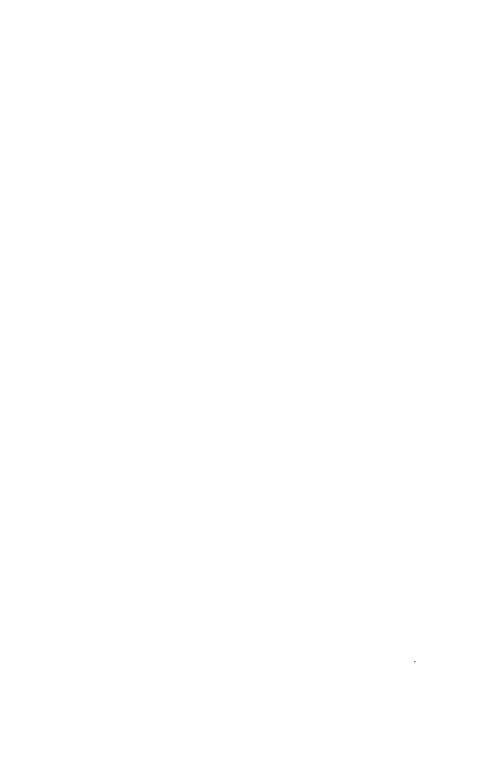
Unfortunately, in China and Japan patients usually apply for treatment only when in the advanced stages; in these the intestinal ulceration and hepatic cirrhosis are generally so pronounced that drug treatment is of little avail. Miracil D, when tested by Vogel and Minning, is not satisfactory and less effective than in S. mansoni. Clinical trials by Pesigan in man were similar.

As in Egyptian splenomegaly (p. 728) splenectomy has been performed, but usually with little success, the hepatic cirrhosis being too far advanced. Campbell suggested that, if the blood-platelet count rises after the delivery of the spleen during operation, the splenic artery should be tied, and the spleen returned into the abdominal cavity, and that this procedure obviates operative shock.

Emetine.—Injections of emetine hydrochloride are as efficacious as in the other schistosome infections; but it is necessary to remember that, as has been shown experimentally in goats infected with the allied Schistosoma spindale, fatal thrombosis of pancreatic and portal veins, as the result of the presence of dead parasites, may ensue.

Prophylaxis.—Water reported to cause the disease should be boiled, or avoided, for drinking or bathing purposes. Sportsmen, if they must frequent such regions, should wear rubber boots or waders. It must be remembered that the snail hosts are amphibious. Lime in a solution of 1 in 1,000 is the most economical reagent for the extermination of the intermediary host and kills cercariæ in thirty minutes. It is especially recommended because of its added value as a fertilizer. Miyajima advocated damming up ditches for twenty-four hours and the addition of quicklime to make up a 1 per cent. solution for ten hours, whilst those outside the ditches are killed with a steam jet. Copper sulphate, 1 in 200,000, is toxic for these snails, but they may also be kept in check by training coolies to collect them. It is said that eggs of the parasite remain viable for ten days outside the body in solid fæces, and this factor should be recognized in formulating sanitary measures. Wright has summarized methods of control: (1) chemical treatment of night soil to render the

eggs non-viable; (2) paving of drainage ditches of irrigation channels and removal of vegetation from the banks to facilitate the flow of water; (3) large scale treatment of infected persons; (4) control of infection of reservoir hosts; (5) education to limit the practice of promiscuous defecation and prevention of the custom of bathing and washing cloths in infested waters; (6) the use of molluscicides. The prophylaxis of this form of schistosomiasis presents many difficulties, for the disease attacks domestic animals, especially dogs, as well as man. The snail vectors, moreover, live in almost inaccessible situations in channels, overhanging banks and ditches, and, being operculated, can withstand drought with impunity. It has been shown by Rose that those snails which are heavily infected do not propagate, as infection with cerearia destroys the genital glands. The most successful molluscicides are dinitro-o-cyclo-hexylphenol and its dicyclohexyl-amine salt which destroy not only the snails but also eggs and cercariae of S. japonicum.



CHAPTER XLV

PARASITES OF THE LYMPHATIC SYSTEM AND CONNECTIVE TISSUES: FILARIASIS

Definition.—Morbid conditions produced by certain nematode worms, or filariæ, the adults of which, of both sexes, live in the lymphatics, connective tissues or mesentery, producing live embryos, or microfilariæ, which find their way into the blood-stream where they are capable of living for a considerable time without developing further.

The embryonic form is referred to in this manual as microfilaria bancrofti (Fig. 152, 1); the other filariæ of the blood are named microfilaria loa (or mf. diurna) (Fig. 152, 2), microfilaria malayi (Fig. 152, 3), microfilaria volvulus (Fig. 152, 4), microfilaria ozzardi (mf. demarquayi) (Fig. 152, 6), and microfilaria perstans, the embryo of *Dipetalonema perstans* (Fig. 152, 5).

Pathological importance.—Only some of these parasites, so far as we know at present, have important pathological bearings, notably, W. bancrofti, IV. pacifica and W. malayi, which, in their adult stages, inhabit the lymphatics of man. There is abundant reason to believe that they are the cause of endemic chyluria, of various forms of lymphatic varix, and of other tropical diseases, including tropical elephantiasis. Loa loa and Onchocerca volvulus produce less serious pathological lesions.

The filariæ less important from a pathological standpoint are dealt with in the Appendix (pp. 995-999).

I. FILARIASIS DUE TO WUCHERERIA BANCROFTI

Geographical distribution and prevalence.—Wuchereria bancrofti occurs indigenously in almost every tropical and subtropical country, from Charleston in the United States and Southern Spain in Europe to Brisbane in Australia. It is extremely common in India and South China, where in some areas nearly 60 per cent. of the inhabitants are affected. It is also found in the West Indies, South America, North Africa, Southern Sudan, West and Central and East Africa (Map VIII). The form in Samoa, Fiji and other Pacific Islands, produces widespread disease, and is known as W. pacifica.

If the individuals who exhibit the microfilaria in their blood be reckoned in addition to those who exhibit the pathological effects of filarial disease, but in whose blood the microfilaria is no longer to be found, the incidence of filarial disease in some of the Pacific islands is very high—as high as 80 per cent.

Ætiology. Parental forms.—The parent filariæ (Wuchereria bancrofti) and the Pacific form (W. pacifica) have been found many times. They are long, hair-like, transparent nematodes, 2–3 in. in length (Figs. 153, 154). The sexes live together, often inextricably coiled about each other. Sometimes they are enclosed, coiled up several in a bunch and tightly packed, in little cyst-like dilatations of the distal lymphatics (Maitland); sometimes they lie more loosely in lymphatic varices; sometimes they inhabit the

larger lymphatic trunks between the glands, the lymphatic glands themselves and, probably not infrequently, the thoracic duct.

The female worm is almost twice the length of the male, and considerably broader. The fully-mature and fecundated female filaria gives birth during her lifetime to an unending stream of living embryos, or microfilariæ, which

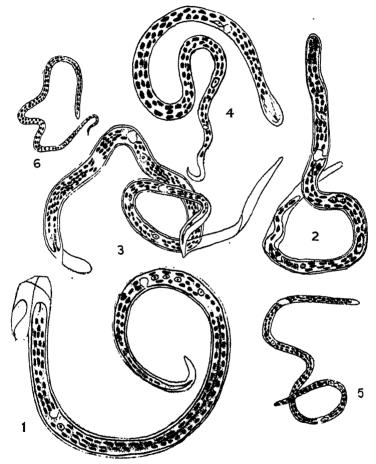


Fig. 152.—Human microfilariæ; 1, Mf. bancrofti; 2, Mf. loa; 3, Mf. malayi; 4, Mf. volvulus; 5, Mf. perstans; 6, Mf. ozzardi. (Drawn to scale.)

emerge from the vaginal orifice. That of W. pacifica, both male and female, are smaller and there is some minor morphological distinction. (For further details see Appendix, p. 993.)

Opportunities have arisen for the study of the life history of W. pacifica in over 1,000 marines who have returned to America from Samoa. After 3-6 months' residence there acute manifestations of filariasis resulted. Immature

worms have been removed from fugitive swellings in the subcutaneous tissues, but very few microfilariæ have been discovered in the blood. This is consistent with the view that it takes approximately one to one and a half years to complete development in the human body (Faust, 1944). (See also p. 744.)

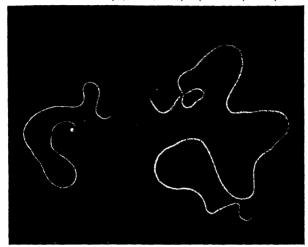


Fig. 153.—Wuchereria bancrotti (enlarged), left, male; right, female. (Dr. M. Oesterlein.)



Fig. 154.—Wuchereria bancrofti (natural size), left, male; right, female.

The life-spans of W. bancrofti and its microfilariæ have not been finally determined. From the fact that the microfilariæ have been found in the blood long after the opportunity of infection has passed, it is concluded that the adults may live for twelve years or longer. The embryo filariæ sometimes disappear completely from the circulation within a few hours of the death of the parent worms during an attack of lymphangitis.

As shown by Wise and the Editor, the mature worm becomes cretified after its death, and may be found in this condition in the lymphatic vessels and glands, sometimes in large numbers (Fig. 155), and it has been found by the Editor originally, later by O'Connor and Elsbach, that the adult filariæ, whether alive or dead, cause occlusion of the lymph vessels and thereby contribute towards general lymph stasis.

According to O'Connor, microfilariæ are destroyed in the substance of the lymphatic glands and are responsible to some extent for the pathological changes found in these structures. He showed that they are broken up in the lymph-node sinuses; and that this is the common method of destruction of foreign substances in lymph-glands has been demonstrated by Indian-ink injection methods by Drinker, Wislieki and Field. McMullen (1937) described a case in an Indian, infected with W. bancrofti, in whom the microfilariæ were detected, by means of the slit lamp, in the anterior chamber of the eye. No visible eye lesions were present.

The microfilariæ.—When present in large numbers in the blood-stream, microfilariæ may be recognized in wet film preparations; but, when the parasites

are scanty, or for the examination of a large number of persons, it is often necessary to examine a considerable quantity of blood (20 c.mm.) in thick-drop preparations, dried and then dehæmoglobinized. When seen in fresh blood the embryo filaria is a snake-like organism which, without materially changing its position, wriggles about very actively.

When dead and stained, the embryo is seen to be enclosed in a sheath (Fig. 156). On measurement, it is found to be about 280 μ by 7 μ .

At the anterior extremity of the living microfilaria can be seen a minute spicule, which is shot out and as rapidly retracted, and it is thought by some that the head is sheathed by a serrated "prepuce." In a fresh blood preparation the spicule can be seen disturbing cells at some distance away.



Fig. 155.—Calcified Wuchereria pacifica lying in and blocking a lymphatic vessel.

The utility of this mechanism is not known. Manson, who observed a similar mechanism in other microfilariæ, including those of birds, suggested that they subserved a necessary function in periodicity—the microfilariæ being enabled to affix themselves to the walls of the capillaries by these means, thus enabling them to maintain their station in the blood-stream during the hours of daylight.

Brug and Rodenwaldt described in the Dutch East Indies the embryo of another filaria (Wuchereria malayi) which has a wide range in Malaya, Ceylon, India, Dutch East Indies, Indo-China, and South China (Fig. 152, 3). Development takes place in a number of mosquitoes of the genera Mansonioides and Anopheles. The adult stage of W. malayi was described by Rao and Maplestone in 1938. In the Pacific form, W. pacifica, development takes place in Aedes scutellaris pseudoscutellaris and A. polynesiensis.

Filarial periodicity.—A singular feature in the life of the microfilaria is what is known as "filarial periodicity." (See also p. 741.)

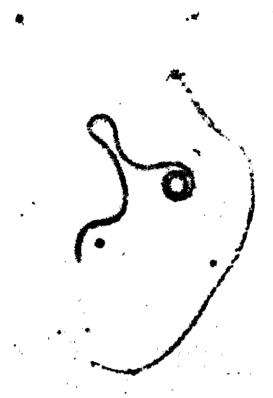


Fig. 156.—Microfilaria pacifica in hydrocele fluid. The embryo on the right has escaped from its sheath.

If, under normal conditions of health and habit, the blood be examined during the day, the microfilaria is rarely seen, or, if it be seen, only one or

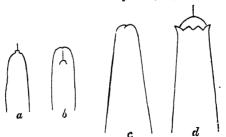


Fig. 157.—Structure of head end of Microfilaria perstans (a, b) and of Microfilaria bancrofti (c, d).

two specimens at most are encountered in a slide. But towards evening they begin to appear in gradually increasing numbers. The swarm goes

on increasing until about midnight, at which time it is no unusual thing to find as many as three hundred, or even six hundred, in every drop of blood; so that it has been calculated that as many as forty or fifty millions are simultaneously circulating in the blood-vessels. After midnight the numbers begin gradually to decrease; by eight or nine o'clock in the morning the microfilariæ have disappeared from the peripheral blood for the day. This nocturnal periodicity, under normal conditions, is maintained with the utmost regularity for as many as twelve years, as in the cases recorded by the Editor. Should, however, as Mackenzie has shown, a filarial subject be made to sleep during the day and remain awake at night, after a period of three to four days the periodicity is reversed;

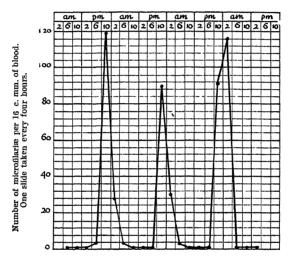


Chart 28.—Filariasis (W. bancrofti, Microfilaria nocturna), showing nocturnal periodicity.

that is to say, the parasites come into the blood during the day and disappear from it during the night. It cannot be the sleeping state, as some have conjectured, that brings about this periodicity; for the ingress of the microfilariæ into the peripheral blood commences three or four hours before the usual time for sleep, and the egress several hours before sleep is concluded, and this egress is not complete until several hours after the usual time of waking. This night swarming of the embryos of W. bancrofti in the peripheral circulation has been regarded as an adaptation correlated to the life-habits of its liberating agent, the mosquito, Culex fatigans, its usual intermediary host. (Chart 28.)

This periodicity is maintained in the absence of the adult parasites, and is therefore a character inherent to the microfilariæ, as was demonstrated by Knott (1935) in a patient transfused with microfilariæ-containing blood and in whom they maintained nocturnal periodicity for fourteen days. Hawking's results (1940) were less conclusive in this species, but Gönnert in a self-transfusion experiment with 160 ml. of blood

containing embryos of L. loa and A. perstans found that the former persisted for four days and retained their diurnal periodicity, whilst the latter persisted in the blood for nearly three years.

Many years ago Manson had an opportunity of ascertaining that during their diurnal temporary absence from the peripheral circulation the microfilariæ retire principally to the larger arteries and to the lungs, where, during the day,

they may be found in enormous numbers.

Low, the Editor and Walters showed that, though the periodicity curve is absolutely nocturnal, yet embryos may be present in small numbers in the peripheral blood in the daytime. The evening rise of the embryo filariæ is much more gradual than the matutinal fall, and the maximum migration occurs at 2 a.m. A fall ensues, however, immediately the waking state is entered upon. The number of microfilariæ in an infected patient remains remarkably constant: Low and the Editor observed the periodicity curve maintained at the same level in one case for a period of twelve years.

Various theories have been advanced by Fülleborn and others to account for this singular phenomenon, though none are entirely satisfactory. Yorke and Blacklock thought that obstruction to the passage of microfilariæ through the cutaneous vessels is at a minimum at the end of the period of bodily activity, and that the periodicity is primarily dependent upon the variations in the actual supply of microfilariæ to the cutaneous vessels. It has also been demonstrated that the periodicity of the filaria of the American crow is to some extent affected by light and darkness. Hawking has shown that acid intravenous infusions cause an increase of microfilariæ in the capillary blood, whilst alkaline ones may cause the reverse.

Gaillard in Indo-China has recently proved that the surgical removal of ten fecund parturient female $W.\ bancrofti$ makes no appreciable difference to the microfilarial curve, but that profound physiological disturbances seriously affect filarial periodicity. Kubo has actually shown that in $Dirofilaria\ immitis$ of the dog there is also a seasonal variation, and that in China the maximal numbers of microfilariæ are found in the circulation during the hot weather at the end of August and beginning of September: the minimal numbers in November and December. In $D.\ repens$, and in $D.\ inimitis$ of the dog the nocturnal periodicity is relative.

Considerable light has been shed upon the mechanism and periodicity by the discovery by Hawking and Thurston of a non-sheathed nocturnal microfilaria in a monkey, Macaca speciosa. In this animal as in man the curve of microfilarial density in the venous blood follows closely that of the capillary blood. They have shown that the increase of microfilaria in the blood at night is not a spurious effect due merely to the congregation of the organisms in the capillaries of the skin, but to a true increase affecting all the circulating blood. It is due to the periodic liberation from accumulations in the small blood vessels of the lung. The mechanism by which this is brought about is unknown. The nocturnal habit is retained by microfilariæ when transfused into another monkey. Nocturnal periodicity is a specific character.

The periodicity of microfilaria is a mechanism by which a compromise is arranged between the two requirements of the microfilaria of optimum survival and transmission. They therefore circulate in the blood where the appropriate insect bites and spends the rest of the twenty-four hours enjoying the favourable conditions of the lung.

Non-periodic microfilaria bancrofti.—Formerly it was thought that nocturnal periodicity was uniformly observed by microfilariæ of W. bancrofti at all times and in every country. Many years ago Thorpe remarked that in Tonga and Fiji the microfilaria could be found often in great abundance in the blood during

the day as well as in the night, but, strange to say, it has since been ascertained that the microfilariæ of neighbouring islands in the Pacific—namely, the Solomons, New Guinea and of the Bismarck Archipelago—are nocturnal periodic.

The Editor demonstrated that the microfilariæ of Indian immigrants who have acquired their filarial infections in India retain their periodic habits during at least three years of residence in Fiji, but that if an Indian or a Solomon Islander acquires the infection in Fiji the microfilariæ are non-periodic in habit.

As an explanation of this striking anomaly, the non-periodic microfilaria is the progeny of a parent worm specifically distinct from W. bancrofti, for which the specific name pacifica is now suggested by the Editor, Muggleton and Buckley, which produces certain pathological peculiarities such as elephantiasis of the arms. Fülleborn and the Editor, after minute study and comparison of the microfilarize



Fig. 158.—Section of lung showing microfilariæ in alveolar capillaries. (Microphotograph: Dr. Spitta.)

from these countries, found that they are morphologically identical. It had been suggested that the non-periodic habit of the Pacific microfilaria is a partial adaptation to the day-habit of the intermediaries of the parasite in Fiji and other islands of the Western Pacific—Aëdes scutellaris pseudoscutellaris and A. polynesiensis. The significant fact that the range of the non-periodic filaria is almost co-extensive with that of these mosquitoes in the Pacific has been established.

The habitat of microfilariæ.—In lung sections (Fig. 158) the microfilariæ lie outstretched or variously coiled in the vessels, large and small. In the heart-muscle they are found in the capillaries between the fibres; in the kidneys they seem especially to affect the Malpighian tufts; a very few are also found in the capillaries of the brain; vast numbers are present in smears from the inner surface of the carotid arteries. Preparations afford no explanation of how the microfilariæ contrive to maintain their position in the blood-current, or of the forces determining their peculiar distribution.

Subsequent observations have shown that, though microfilarize can be demonstrated in the capillaries of the liver and spleen in small numbers, the capillaries of the lung (Anderson) appear to be the favourite habitat of the

embryos of W. bancrofti and of other species which do not exhibit this extraordinary nocturnal periodicity. Thus, the non-periodic Pacific microfilaria has also been found in greatest abundance in these situations.

Hawking and colleagues (1948) have shown that in the filaria of the cotton rat -Litomosoides carinii—the microfilariæ in the bloodstream are reinforced from reservoirs in the pleural spaces.

The mosquito the intermediary host of W. bancrofti.—If the females of certain species of mosquito (Culex fatigans) which have fed on the blood of a filariainfected person are examined immediately after feeding, the blood in the stomach will be found to harbour large numbers of living microfilariæ, while a few hours afterwards many of them will be seen actively endeavouring to escape from their sheaths. Change in the viscosity of the blood seems to prompt them to escape. After a time the majority succeed in effecting a breach and in wriggling themselves free from the sheaths which had hitherto enclosed them (Fig. 159). This process can be induced by chilling wet blood preparations on ice and then allowing them to thaw at room-temperature. The microfilariæ now, having become free, move about from place to place. At a somewhat later period it will be observed that, after discarding their sheaths, they have quitted the stomach and entered the thoracic muscles of the mosquito, where they may be seen moving languidly. To detect this, the insect should be dissected in normal saline solution, for, if distilled water is used, the larvæ break up. In the thorax of the insect the parasite enters on a metamorphosis which takes from ten to twenty days (according to atmospheric temperature) ending in the formation of a mouth, an alimentary canal, and a peculiar trilobed caudal end, as well as in a relatively enormous increase in size (to 16 in.) and activity. During this period the larva

sheds its cuticle (ecdysis) twice. The larval filariæ now leave the thorax, and the majority pass forwards by the prothorax and neck, and, entering the head, coil themselves up close to the base of the proboscis beneath the pharynx and cephalic ganglia, though a few find their way into the abdomen, and even into the legs. Low first showed that the filaria, in its future progress, enters the proboscis, where, as pointed out by Grassi, its exact position is the interior of the proboscis-sheath (labium)

(Fig. 160).

The parasites remain in the proboscis, awaiting an opportunity to enter a warmblooded vertebrate host when the mosquito next feeds. This they appear to do by penetrating the thin membrane that unites the labella to the tip of the proboscis-sheath, and so pass on to the surface of the skin, which they penetrate in the neighbourhood of the puncture made by the mosquito. As pointed out by Annett and Dutton, there is a weak point in the chitinous skeleton of the labium just where the labella are joined on, and it is at this spot that the parasites escape. Sometimes the larval filaria, in its progress through the thorax, becomes arrested and dies; the

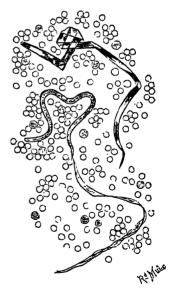


Fig. 159.-Microfilariæ casting their sheaths.

defunct worm then appears to become enclosed, like a mummy, in a case of chitin inside the mosquito's body, resulting in the curious structure represented in Fig. 161. The physical conditions for development are important. The optimum is between 70 to 90° F. and 70–100 per cent. humidity. The highest infectivity rate is obtained when the microfilariæ in the imbibed blood number 100–150 in 0.2 ml.

Mechanism of blood suction in mosquitoes.—Fülleborn concluded that bloodsucking in mosquitoes is a reflex action. The fluid is aspirated by the initiatory



Fig. 160.—W. bancrofti in head and proboscis of mosquito. (G. C. Low.) a, a, a, Filariæ; b, labium; c, labrum; d, base of hypopharynx; e, duct of veneno-salivary gland; f, f, cephalic ganglia; g, g, eye; h, cesophagus; f, pharyngeal musele.

gulp-like working of the insect's sucking pump, and when the mouth cavity is full of fluid, the spasmodic action of the pump becomes converted into a more or less continuous flow until the abdomen is fully distended. This was later confirmed by Macgregor.

These observations prove that, like the malaria parasite, the filaria is introduced into its human host through the agency of a mosquito-bite. Once introduced



Fig. 161.—Chitinized filaria in thorax of mosquito.

into the human body, the filaria finds its way into the lymphatics and glands, where it attains sexual maturity in five to eighteen months (Wartman, 1947). In American marines in Samoa adult worms were recovered within three months of first exposure¹. In due course new generations of embryo filariæ (microfilariæ)

are poured into the lymph. These, passing through the gland—if such should intervene—by way of the thoracic duct and left subclavian vein, or by the lymphatics of the upper part of the body, finally enter the circulation.

Epidemiology and endemiology.—In most countries in which

An extensive study was made by W. B. Wartman of filariasis in the recent war in the Pacific (1947)

Medicine 28, 4, 333.

filariasis is common it appears to be the rule that the incidence of infection is greatest in the male, though in British Guiana Daniels and Conyers found twice as many females infected as males. This exception to the general rule probably finds an explanation in the habits of the natives who are infected at night in their houses, especially in Georgetown. The Editor's statistics from Fiji showed that of 1,320 people of Fijian blood, 30.4 per cent. of males and 23.9 per cent. of females were filariated. The incidence is greatest in both sexes after the twentieth year; comparatively more females than males are infected below the age of ten. The youngest infected patient—a child of 14 months—was recorded by Anderson in British Guiana.

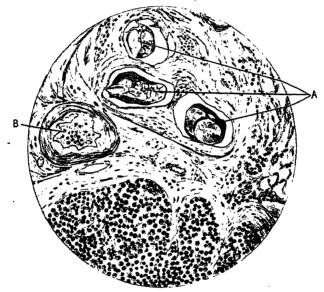


Fig. 162.—Section of a fibrosed lymphatic gland.
A, Portions of a calcified W. pacifica: B, partially occluded lymphatic vessel.

The rate of filariation varies considerably in different islands of the Pacific, even in different districts of the same island, and is in direct proportion to the incidence of elephantiasis and other filarial diseases. In 1912 in Ceylon the Editor found that, whereas 26 per cent. of the adults of some villages were infected, in neighbouring hamlets the inhabitants were quite free from these parasites and their associated diseases. Probably this inequality may be due to infections with W. malayi, and can be explained by proximity to tanks and pools where mosquitoes breed.

Pathology.—The filaria not generally pathogenic.—In most cases of filarial infection the parasite exercises no manifest injurious influence whatever. In a certain proportion, however, there can be no doubt that it does exert a prejudicial effect, and this mainly by obstructing lymphatics. Healthy, fully-formed microfilariæ—that is to say, the embryonic filariæ in the blood—are, so far as we can tell, harmless.

Filarial disease originating in injury of lymphatic systems.—Roughly speaking, the filaria causes two types of disease: one characterized by varicosity of lymphatics, the other by more or less solid cedema. The exact way in which the parasite operates has not been definitely and absolutely ascertained for all types of filarial disease. Apparently, in some instances a single worm, or a bunch of worms, may plug the thoracic duct, and act as an embolus or originate a thrombus; or, the worm may give rise to inflammatory thickening of the walls of this vessel, and so lead to obstruction from the consequent stenosis or thrombosis. In other instances the minor lymphatic trunks and the glands may be similarly occluded. (Fig. 162.)

The Editor demonstrated in Fiji that the afferent lymphatic glands situated at some considerable distance from the actual seat of the filaria worms (for instance, the lumbar glands) undergo considerable changes, such as fibrosis, focal necrosis, giant-cell formation, macrophage proliferation and aggregation of small epithelioid foci, changes which are also seen in the lymphatic vessels and periglandular connective tissues. The resemblance to tuberculoid focal granulomata is close (Thompson, Rifkin and Zarrow). These changes may be due partly to the destruction of microfilarize within the gland substance, or to toxins excreted by the

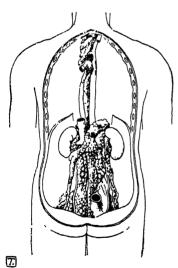


Fig. 163.—Dissection of the lymphatics in a case of chyluria, showing the dilated right and left renal lymphatics and the thoracic duct. (Mackenzie, "Trans. Path. Soc. Lond.")

adult parasites. Some microfilaria undergo calcification, and thereby cause endothelial proliferative outgrowths in the lymphatic channels. There now appears to be little doubt that the pathological effects produced by W. pacifica are more severe and extensive than those due to W. bancrofti.

Early manifestations have been well described by American observers in the Pacific area in marines and soldiers. They are allergic in nature and consist of fugitive, tender and painful swellings like erythema multiforme, especially on the arms. lymphadenitis also of the neck, axilla and groin. Biopsy studies show changes similar to those produced by injections of D. immitis antigens. When the parent worms are bunched together lymphangitis appears with the liberation of microfilarize into the tissues. Associated with these phenomena are generalized pains, testicular pain and funiculitis. Moderate emacia-

tion results (Leede and Josey, 1945). Hypersensitivity is probably the explanation of most of these phenomena and the intradermal test is usually positive.

Classification of the pathological manifestations is difficult. Clinton Manson-Bahr has suggested division into three stages: primary or allergic; secondary or carrier: and tertiary or obstructive.

The primary or allergic stage may be simulated by injection of Dirofilaria immitis antigen and consists of eosinophilic infiltration of glands and subcutaneous tissue around the immature filarial worms. In this manner lymphangitis, funiculitis and orchitis are brought about.

The secondary or carrier stage may last from two to seven years after infection—that is till the filarial worms have matured and the microfilariæ have entered the circulation as was shown by Michael and Neumann in American soldiers infected in the Pacific in the recent war.

The tertiary or obstructive stage is caused by destruction of the lymphatic filter of the lymph glands with consequent blocking and dilatation of the lymphatics. As a result of the lymphatic obstruction there occurs a transudation into the tissues of lymph rich in protein which causes a cellular proliferation of the connective tissues with the production of elephantiasis.

Pathology of lymphatic varix.-In consequence of the rich anastomosis between contiguous lymphatic areas, a compensatory lymphatic circulation is sooner or later established. But before this can be thoroughly effected a rise of lymph-pressure and a dilatation of the lymphatics in the implicated area must take place. This leads to lymphatic varix of different kinds, degrees and situations. When the seat of filarial obstruction is the thoracic duct, the chyle poured into that vessel can reach the circulation solely by a retrograde movement; this fluid may therefore be forced to traverse in a retrograde way the abdominal and pelvic lymphatics, the lymphatics of the groin, scrotum, and abdominal wall. As a consequence, these vessels, together with the thoracic duct up to the seat of obstruction, become enormously dilated. In dissection of such cases (Fig. 163) the thoracic duct has been found distended to the size of a finger, the abdominal and pelvic lymphatics forming an enormous varix, perhaps a foot in diameter and some inches in thickness, concealing kidneys. bladder, and spermatic cords. In such cases, when one of the vessels of the varix is pricked or ruptures, the contents are found to be white or pinkish. They are not limpid like ordinary lymph. They are chyle, therefore—chyle on its way to enter the circulation by a retrograde compensatory track. When the varix involves the integuments of the scrotum, the result is "lymph scrotum"; when most prominent in the groin, then a condition of glands is produced which Manson termed "varicose groin-glands"; when the lymphatics of the bladder or kidneys are affected and rupture from over-distension, then chyluria is the result; when those of the tunica vaginalis rupture, then there is chylous dropsy of that sac—"chylocele"; but when rupture is into the peritoneum—chylous ascites. Occasionally, varicose lymphatic glands resembling those in the groin are found in the axilla. Occasionally, also, limited portions of the lymphatic trunks of the limbs are similarly and temporarily, or more permanently, distended. This, doubtless, is the pathology of all those forms of filarial disease characterized by visible varicosity of lymphatics, with or without lymphorrhagia. It may happen that the obstruction is in some lymphatic tract on the distal side of the entrance of the chyle-bearing vessels into the receptaculum chyli. In this case a rupture of the consequent lymphatic varix will give issue to a limpid lymph unmixed with chyle.

In filarial disease associated with lymphatic varix, microfilariæ are generally present in the blood as well as in the contents of the dilated vessels. Sometimes,

it is true, the microfilariæ are not found. Such cases are probably of long standing; had the microfilariæ been looked for at an earlier stage of the disease, they would presumably have been discovered.

The microfilaria have been seen to vanish from the blood-stream by several observers; doubtless this is due to the death of the parent parasite, and is generally associated with an attack of lymphangitis.



Fig. 164.—Section of a thickened brachial lymphatic containing portions of dead filariæ undergoing disintegration and blocking the lumen of the vessel. Note the large amount of fibrosis.

Pathology of elephantiasis.—Reasons for regarding elephantiasis as a filarial disease.—(1) The geographical distribution of W. bancrofti and that of elephantiasis correspond; where elephantiasis abounds, there the filaria abounds, and vice versa. (2) Filarial lymphatic varix and elephantiasis occur in the same districts, and frequently in the same individual. (3) Lymph scrotum, unquestionably a filarial disease, often terminates in elephantiasis of the scrotum, (4) Elephantiasis of the leg sometimes supervenes on the surgical removal of a lymph scrotum. (5) Elephantiasis and lymphatic varix are essentially diseases of the lymphatics. (6) Filarial lymphatic varix and true elephantiasis are both accompanied by the same type of recurring lymphangitis. (7) As filarial lymphatic varix is practically proved to be caused by the filaria, the inference

appears to be warranted that, with rare exceptions, the elephantiasis of warm climates—the disease with which lymphatic varix is so often associated and has so many affinities—is attributable to the same cause.

In filariated subjects a process of proliferation of the endothelium of the lymphatic vessels takes place—a species of lymphangitis, first described by the Editor and later confirmed by O'Connor; it is due to the action of the microfilariæ which become imprisoned in the endothelial lining of the vessel (Fig. 165), and is probably fostered by the stimulating action of the lymph upon cellular proliferation.

There is quite enough evidence to show that the true pathological basis of elephantiasis lies in the destruction and blockage of the lymphatic filters in the lymphatic glands.

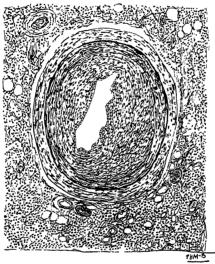


Fig. 165.—Occlusion of lymphatic vessels by proliferation of the endothelium in filariasis (obliterative endolymphangitis).

For the true understanding of elephantiasis it is necessary to give a few facts about the known physiology of the lymphatic system. Lymph is a transudation from the veins and its production is maintained and regularized by intravenous pressure. It appears that, in order to produce true elephantoid tissue, a transudation of lymph must take place, and that this transuded lymph must contain an excess of protein; this forms an ideal culture medium for proliferating cells, thereby producing lymphous hyperplasia.

Diagnosis.—Diagnosis is made by demonstration of the microfilariæ in the night-blood; usually 20 c.mm. are necessary for the purpose, the thick-drop method being employed (see p. 1074). But for reasons already stated the embryos may not always be present. There is usually an appreciable eosinophilia which is most marked in the allergic stage.

Knott's method of concentrating the microfilariæ is most useful in scanty infections and for conducting filarial mass surveys. This consists of abstracting 1 ml. of venous blood from the antecubital vein. This is diluted in 2 per cent. formalin in distilled water 9 ml. and then centrifuged. The microfilariæ are found massed in the precipitate.

Serological and intradermal tests in filariasis.—These tests were introduced by Fairley, Taliaferro and Hoffman. The antigen is prepared from Dirofilaria immitis of the dog, Dracunculus medinensis or Setaria equini of the horse diluted 1:4,000-1:8,000, which is washed and dried, it being estimated that 1 grm. is extracted from 250-300 worms. An alcoholic is more potent than a saline extract of the antigen. A positive complement-fixation is given with most cases of W. bancrofti filariasis; but it is a group reaction, and appears to be more reliable in L. loa than in W. bancrofti, but is also positive in Onchorerca volvulus. Lloyd and Chandra obtained the most reliable results with an antigen derived from the acctone-insoluble lipoids of D. immitis by the process used by Bordet for syphilitic antigen. Mohr and Lippelt obtained similar results with an antigen prepared from the filaria of the South American ostrich, Controtospiculum rhex. Recently, extracts of the filaria of the cotton rat—Litomosoides carinii—have been prepared and give positive reactions in 77 per cent. (Goodman et al. 1945).

The intradermal test is based on the same immunological principles. Fairley uses 0.25 ml. of a 0.1 per cent. extract as antigen. An immediate (30 min.) and delayed reaction are obtained; the latter may become indirect after a period of forty-eight hours. A wheal over 2 cm. in diameter is regarded as positive. Antigen controls should be instituted by similarly diluted dog and horse protein. Opinions vary about the reliability of this test. In the Pacific it is vitiated by the concurrence of intestinal nematode infections. Leligs (1947) concludes that, though in some degree, diagnostic, this test cannot be wholly depended upon. On the other hand, Wharton (1947) finds that cross reactions with intestinal helminths are not infrequent. The immediate reaction is erythema from 1-4 cm. in all degrees to wheals with pseudopodia. It takes 15 min. to 1 hour to develop: the delayed reaction takes place after 24 hours with cedema.

Technique. Preparation of antigen for complement-fixation test.—Technique similar to that described for schistosome cercarial antigen is employed, 0.5 grm. of the dried powdered Dirofilaria immitis being extracted with 50 ml. of 98 per cent. alcohol for 24 hours at 37° C. Well shaken by hand several times during this period, it is filtered through Whatman No. 1 and a Buchner filter. The filtrate is subsequently concentrated by bubbling air through the solution kept at a temperature of 40° C. by immersion in a water-bath till turbid; this turbidity is then removed by adding 8 ml. of fresh alcohol, making the total volume 25 ml. The resulting extract is then stored in the ice-chest in amber-coloured ampoules of 1 ml. capacity. The technique of putting up the test is similar to the standard advocated for serological diagnosis of schistosomiasis.

Preparation of antigen for intradermal test.—Fifty ml. of a 1 per cent. saline extract of dried powdered antigen is incubated for two hours at 37° C., being well shaken by hand from time to time. Subsequently it is passed through a Whatman No. 1 filter paper, then through a Buchner filter, and is then sterilized by passage through a sterile Seitz asbestos filter. The filtrate is put up in dark glass ampoules and stored on ice.

Pandit's reaction is an adhesion phenomenon. When blood containing microfilariæ is mixed with blood from a normal person and kept at room temperature for an hour or longer, the embryos become sluggish and surrounded by adherent leucocytes.¹

Filarial elephantiasis.—The anatomical situation of elephantiasis depends upon the distribution of the afferent lymphatic vessels. It must not be thought, however, that lymphatic elephantiasis is *solely* the product

¹ The "Thorn" test is applicable to filarlasis - i.e., if the cosmophilia in the blood remains at the same figure after injection of 25 mgm, of cortisone or A.O.T.H.

of filarial infection. The following classification of elephantiasis has been suggested:

- (a) Congenital or familial elephantiasis (Milroy's or Meige's disease); stenosis of main lymphatic trunks.
- (b) Parasitic elephantiasis: Wuchereria bancrofti, W. pacifica, W. malayi, or Onchocerca volvulus.
- (c) Septic elephantiasis (*Elephantiasis nostras*—lymphatic infection by streptococci).
- (d) Toxic elephantiasis due to absorption of irritating toxins, such as chrysarobin.
- (e) Obstructive elephantiasis, due to tuberculous glands, carcinomatous growths, lymphogranuloma syphilis, or yaws, or to surgical removal of main lymphatic glands.
- (f) Venous elephantiasis, secondary to venous thrombosis, such as phlegmasia alba dolens, or white leg.

Tesch, Brug and others have shown that elephantiasis is also produced by Wuchereria malayi. The difference between the two forms of lymphatic obstruction seems to lie in the predilection of this parasite for the legs rather than for the genitalia and scrotum as in Wuchereria bancrofti infestation.

In most cases the real origin of the obstruction lies in the fibrotic changes induced by the parasite in the lymphatic vessels and glands, leading to elephantiasis. Lymph stasis in lymphatic vessels alone does not produce elephantiasis; this has been proved by ligature of the lymphatic trunk, which results in œdema, but not in true elephantoid hypertrophy.

Anderson believed that the adult filariæ living in the lymphatic system, by the damage they produce in the intima of the vessels, so prepare the way that a streptococcal or staphylococcal infection, however mild, is able to contain a foothold and that by the changes thus produced the

lymph-channels become further occluded.

O'Connor demonstrated that in filarial lymphangitis focal spots can be distinguished from which the inflammatory process commences, and that this indicates the site of a dead filaria; furthermore, that an attack of lymphangitis may be cut short by injection of sulpharsphenamine (0.2 grm. dissolved in 2 ml. of sterile 1 per cent. novocain). This observer, with Golden and Auchincloss, found that in filariated subjects, especially in elephantiasis, calcified filariæ may be demonstrated by X-rays. The shadows range from 1 mm. in width to 2–3 mm. in length. This seems to indicate that the infection may be quite extensive. Fifteen shadows, or groups of shadows, were detected in one elephantoid leg.

Thus can be explained the production of elephantiasis by the filaria, and the absence from the blood of the embryos of the parasite which started the disease, as they cannot pass the occluded glands. Very likely the parent worm, or worms, die at an early stage of the disease, killed by subsequent

lymphangitis, or some other undetermined cause.

This anomaly is found in other conditions produced by W. pacifica. In Fiji, for instance, the Editor observed that 38.2 per cent. of the cases of elephantiasis harboured microfilariæ, while the microfilaria-rate in glandular enlargement,

also of filarial origin, was 34.6 per cent. On examining all those with clinical manifestations of filarial disease, it was found that 19.7 per cent. thus affected had microfilariæ in the blood, but that 44.8 per cent. of those with numerous microfilariæ showed no obvious sign of disease. As in the case of W. malayi, it is possible that the non-periodic W. pacifica in the Pacific produces its own peculiar pathological picture. This filaria lives mostly in the lymphatic glands and produces phenomena which are connected with these structures. It has a special preference for the epitrochlear glands, and is therefore likely to produce elephantiasis of the arms. It does not commonly produce either chyluria or lymphuria as does the periodic W. bancrofti.

Symptoms, Diagnosis, and Treatment of Filarial Diseases

Enumeration of filarial diseases.—The diseases known to be produced by or associated with W. bancrofti are—abscess; lymphangitis; arthritis; synovitis; abscess of hip-joint; varicose groin glands; varicose axillary glands; lymph scrotum; cutaneous and deep lymphatic varix; orchitis; funiculitis; hydrocele; chyluria; elephantiasis of the leg, scrotum, vulva, arm, mamma, and other parts; chylous dropsy of the tunica vaginalis; chylous ascites; chylous diarrhæa, and probably other forms of disease depending on obstruction or varicosity of the lymphatics, or on the death or injury of the parent filariæ in a lymphatic abscess—including fatal peritonitis and secondary infections by pyogenic microorganisms (filarial abdomen). Cilento has drawn attention to the frequency of adenitis of the popliteal space in filaria-infected children in Queensland.

Abscess.—Occasionally, as already mentioned, whether in consequence of blows or other injuries, of lymphangitis, or of unknown causes, the parent filariæ die. Generally the dead body is absorbed, just as a piece of aseptic catgut would be, or becomes cretified. Sometimes the dead worm acts as an irritant and causes abscess, in the contents of which fragments of the filaria may be found. Such abscesses, occurring in the limbs or scrotum, will discharge in due course or may be opened; if properly treated surgically, they may lead to no further trouble. Should they form in the thorax or abdomen, serious consequences and even death may ensue.

The starting-point of these abscesses is, possibly, a small hæmorrhage produced by the filaria worm which becomes secondarily infected, but when no such occurrence takes place the defunct filaria becomes cretified. This has to be differentiated from tropical pyonyositis. (See p. 693.)

Lymphangitis and elephantoid fever.—Lymphangitis is common in all forms of filarial disease, particularly in elephantiasis, varicose glands, and lymph scrotum. In the limbs it is usually retrograde the characteristic painful cord-like swelling of the lymphatic trunks and associated glands, and the red congested streak in the superjacent skin, are usually apparent at the commencement of the attack. The attack may continue for several days, and be accompanied by severe headache, anorexia, often vomiting, and sometimes delirium. After a time tension of the inflamed integuments may relieve itself by lymphous discharge from

¹ Wise and Minett found filarize, living or cretified, in the following situations: pelvis of kidney (31 times), epididymis (18 times), retroperitoneum (12 times), ilio-psons muscle (4 times), dilisson's capsule (twice), inguinal glands (25 times), lymphatic vessels (8 times). Similar observations were made by the Editor in Fiji.

the surface. Usually, the attack ends in profuse general diaphoresis. Lymphangitis may be confined to groin glands, testis, spermatic cord (endemic funiculitis) or abdominal lymphatics. When it affects an extensive abdominal varix, symptoms of peritonitis rapidly develop, and may prove fatal. The evidence at present available is that lymphangitis represents an allergic response to the presence of adult worms. Winckel and others discount microfilariæ as being involved.

In the Pacific islands a form of filarial fever is commonly met in heavily-infected districts, unassociated with lymphangitis; this probably represents inflammation of the deep-seated lumbar lymphatics or glands. It has been pointed out by Winckel and Fros (1952) that hetrazan treatment

often provokes such an attack.

Diagnosis.—This fever, usually termed "elephantoid fever," occurs at varying intervals of weeks and months, or years, in nearly all forms of elephantoid disease. Its tendency to recur, the severe rigor, and the terminal diaphoresis, caused it to be mistaken for malaria. In Barbados, where there was until recently no malaria, it is habitually called "ague." In Samoa it is known as "mumu fever"; in Fiji as "wanganga." In India, Rao and Sukhatne believed that there exists a periodicity in the incidence of lymphangitis, which is greatest during the monsoon period, July to September, when humidity is high. Cilento has described a form of filarial fever with abdominal implications which is ascribed to lymphangitis of the broad ligament in women. The ligament is thickened and pulpy to palpation. This causes a dragging pain in the corresponding loin and brings about pain in the menstrual period. Diagnosis from chronic salphingitis is difficult. In Queensland filariasis the popliteal gland is frequently enlarged.

Treatment.—Treatment should consist in removing any cause of irritation, in rest, elevation of the affected part, cooling lotions, mild aperients, opium or morphia to relieve pain, and, if tension is great, pricking or scarifying the swollen area under suitable aseptic conditions. Subsequently the parts, if their position permits, should be elevated and firmly bandaged.

Sulphonamides have been used. Sulphathiazole and sulphadiazine and other sulphonamides have been given with apparent success, especially when combined with penicillin. *Antisan*, and other anti-histamine drugs are indicated.

Varicose groin-glands (Fig. 166).—Varicose groin-glands are frequently associated with lymph scrotum, with chylous dropsy of the tunica vaginalis, or with chyluria. Occasionally all four conditions may co-exist in the same individual.

As a rule, the patient is not aware of the existence of varicose glands until they have attained considerable dimensions. Then, a sense of tension, or an attack of lymphangitis, calls attention to the state of the groins, where certain soft swellings are discovered. These swellings may be of insignificant dimensions or they may attain the size of a fist. They may involve both, or only one groin; they may affect the inguinal glands, or the femoral glands alone, or (more usually) both sets together.

Remnants of microfilariæ have been demonstrated within giant cells in

these enlarged glands.

Diagnosis.—It is important to be able to diagnose these tumours from hernia, for which they are often mistaken. This can be done by observing that they are not tympanitic on percussion; that, though pressure causes them to diminish, they do so slowly; that there is no sudden dispersion on taxis, accompanied by gurgling, as in hernia; that they convey a relatively slight or no impulse on coughing; that they slowly subside when the patient lies down, and slowly return, even if pressure be applied



Fig. 166.—Bilateral varicose groin glands with lymph stasis and slight elephantiasis of right leg. (Dr. F. W. O'Connor, Porto Rico.)

over the saphenous or inguinal openings, on the erect posture being resumed. The cautious use of the hypodermic needle will confirm diagnosis, which may reveal microfilaria, or actually filarial eggs, and the diagnosisis further strengthened by the co-existence of lymph chyluria, or chylous scrotum. hydrocele, and microfilariæ in the blood. Chronic swellings about the groin, cord, testis and scrotum in patients from the tropics should always be regarded as possibly of filarial origin.

Treatment.—Unless they give rise to an incapacitating amount of discomfort, and are the seat of frequent attacks of lymphangitis, varicose groin-glands are best left alone. Excision is not always satisfactory, as it may be followed by lymphorrhagia at the seat of the wound, by excessive dilatation of some other part of the implicated lymphatic area, by chyluria, or by elephantiasis of one or both legs.

Similar varicose dilatation of the

axillary glands is sometimes, though much more rarely, found. Bancroft designated varicose axillary and groin glands "helminthoma elastica."

Cutaneous and deeper ymphatic varices.—Occasionally cutaneous lymphatic varices are seen on the surface of the abdomen, on the legs, arms, and probably elsewhere. Filarial lymphangiectasis of the spermatic cord is not uncommon. The contents may be milky and chylous, or straw-coloured and lymphous, according to situation and connections.

Thickened lymphatic trunks.—After the initial swelling and inflammation of lymphangitis have subsided, a line of induration remains. On excising this thickened tissue and carefully dissecting it, minute cyst-like dilatations of the lymphatic involved were found by Maitland, Daniels, and the Editor, and in these cysts adult filariæ, sometimes dead.

Filarial glandular enlargement.—In the Pacific islands great enlargement of the lymphatic glands with fibrotic changes is by far the most frequent symptom of filarial disease. The epitrochlear gland, for instance, is often affected—in Fiji in 22 per cent. of the population.

The groin-glands are often very much enlarged, sometimes to 2 or 3 in. in diameter, and may form permanent tumours in the groin. On section they have the appearance of an unripe pear, the central portion being



Fig. 167.—Pendunculated groin-glands in a Fijian with double varicose hydrocele.

These glands, containing adult δ and Q filarize, were removed at operation. No microfilarize were found in the blood. There were also masses of enlarged glands in the right groin.

fibrotic, the peripheral glandular. The deep-seated glands—iliac, lumbar, mesenteric, and mediastinal—may also be enlarged. On dissection, live filariæ or their calcified remains may be demonstrated. (Fig. 167.) Behm and Hayman (1946) have described the microscopical pathology of these glands. The predominating cell is known as the "littoral cell" in the lymphatics and sinuses. There is also precipitation of acidophilic material about the filaria worm with necrosis, exudation of eosinophils, plasma

cells, lymphocytes, proliferation of macrophages and reticular fibres. Microfilariæ, when present, are also surrounded by an eosinophilic precipitate.

Treatment.—Usually it is inadvisable to remove these glands, seeing that, as with varicose groin-glands, incurable lymphocele might result.

Lymph scrotum (Fig. 168).—In this disease the scrotum is more or less enlarged. Though usually silky to the touch, on inspection the skin presents a few or a large number of smaller or larger lymphatic varies which, when pricked, or when they rupture spontaneously, discharge large quantities of milky or sanguineous-looking or straw-coloured, rapidly-coagulating lymph or chyle. In some cases 8 or 10 oz. of this substance will escape from a puncture in the course of an hour or so; it may go on running for many hours on end, soiling the clothes and exhausting the



Fig. 168.—Lymph scrotum and varicose groin-glands.
(Photo: Dr. Rennie.)

patient. Usually, microfilariæ can be discovered in the lymph so obtained, as well as in the blood. In a large proportion of cases of lymph scrotum the inguinal and femoral glands either on one or on both sides, are varicose.

Treatment.—Unless inflammation is frequent, or there is frequent and debilitating lymphorrhagia, or unless the disease tends to pass into true elephantiasis, lymph scrotum-kept scrupulously clean, powdered with boracic acid, suspended, and protected -had better be left alone. Should it, however, be deemed expedient to remove the diseased tissues, this can be easily done. scrotum should be well dragged down by an assistant while the testes are pushed up out of the way of injury. A finger knife is then passed through the scrotum, and in sound tissues, just clear of the testes, the mass is excised by cutting backwards and forwards. No diseased tissues and hardly any flap should be left. Sufficient covering for the testes can be obtained by dragging on

and, if necessary, dissecting up the skin of the thighs, which readily yields and affords ample covering. It is a very common but a very great mistake to remove too little. As a rule, the wound, if carefully stitched and dressed antiseptically, heals rapidly.

In consequence of this violent interference with a large varix, of which that in the scrotum is but a part, chyluria or elephantiasis of a leg may supervene. The patient should be warned of this possibility.

Chyluria.—When a varix ruptures in the wall of the bladder, or elsewhere in the urinary tract, in the thoracic duct or in the lymphatics of the urinary system, there is an escape of the contents of the lymphatics into the urine. Chyluria is the result. If, as often happens, the urine contains blood, the condition is known as hæmatochyluria.

A curious fact about this form of filarial disease is that in the Pacific islands it is very rare, though quite common in India, China, and North Africa. It frequently appears without warning; usually, however, pain in the back and aching sensations about the pelvis and groins—probably caused by great distension of the pre-existing lymphatic varix—precede it. Retention of urine, from the presence of chylous or lymphous coagula, is sometimes the first indication of serious trouble. Whether preceded by aching, or by retention, or by other symptoms, the patient becomes suddenly aware that he is passing milky urine. Sometimes, instead of being white, the urine is pinkish, or even red: sometimes, white in the morning, it is reddish in the evening, or vice rersa. Sometimes, while chylous at one part of the day, it is perfectly limpid at another. Great variety in this respect exists in different cases, and even in the same case from time to time, depending on temporary closure of the rupture in the lymphatic, and also on the nature of the food1. Chyluria is very likely to occur, either for the first time, or as a relapse, in pregnancy or after childbirth.

Physical characters of chylous urine.—If chylous urine be passed into a urineglass and allowed to stand, within a very short time, as a rule, the whole of the urine becomes coagulated. Gradually, the coagulum contracts until, at the end of some hours, a small, more or less globular clot, usually bright red or pinkish, is floating about in a milky fluid, the appearance of which is entirely due to suspended fat particles. Later, the fluid separates into three layers. On the top there is a cream-like pellicle; at the bottom, a scanty reddish sediment, sometimes including minute red clots; in the centre the mass of the urine forms a thick, intermediate stratum, milky white or reddish white, in which floats the contracted coagulum. If a little of the sediment be taken up with a pipette and examined with the microscope, it is found to contain red bloodcorpuscles, lymphocytes, granular fatty matter, epithelium and urinary salts, and mixed with these in a large proportion of cases, though not in all, microfilariæ. The middle layer contains much granular fatty matter; while the upper, creamlike layer consists of the same fatty material in greater abundance, the granules tending to aggregate into larger oil globules. If a little of the coagulum be teased out, pressed between two slides, and examined with the microscope, microfilariæ, more or less active, may be found entangled in the meshes of the fibrin. According to Yorke and Blacklock, the number of microfilariæ in chylous urine varies greatly within the twenty-four hours in quite an irregular manner. If ether or xylol be shaken up with the milky urine, the fat particles are dissolved out and the urine becomes clear; the fat may be recovered by decanting and

¹ The sanguineous appearance so frequently seen in chylous urine and in other forms of filarial lymphorrhagia possibly depends in some instances on the formation of blood-corpuscles in lymph long retained in the varicose vessels, as a result of the normal evolution of the formed elements in that fluid. In other instances it is probably caused by rupture of small blood-vessels into the dilated lymphatics; in these cases the microfilarise appear in the urine passed during the night-time only.

evaporating the ether, which floats on the urine. Boiling the urine throws down a considerable precipitate of albumin. When the urine contains only lymph, fatty elements are absent, or are present in but very small amount. According to Young, a twenty-four-hour sample of chylous urine contains 1.8–2.6 per cent. of fat. The amount of this substance excreted is generally, though perhaps not invariably, dependent on the amount ingested.

By cystoscopy the Editor has seen in the bladder the chylous vesicles which burst when fully distended, and Romiti showed by this method, as well as by ureteric catheterization, that lymphatic obstruction in a limited portion of the

urinary system suffices to cause chyluria.

Although chyluria is not directly dangerous to life, yet if it is prolonged, it gives rise to pronounced anæmia, with depression of spirits and feelings of weakness and debility, and tends to incapacitate the patient for active,

vigorous life.

Lymphuria.—It would be more correct to describe a certain proportion of filarial cases passing cloudy urine as "filarial lymphuria," as Low and Wise suggested. In these cases the abnormal element is lymph, and there is no trace of fat. Albumin is found in considerable quantity, and blood may be present as well. The chief cellular constituent is the lymphocyte. Low, who was able to investigate one of these cases shortly after death, found the lymphatic obstruction located in the kidney lymphatics, which was due to calcification of dead filariæ.

Treatment.—The treatment of chyluria should be conducted on the same lines as that of inaccessible varix elsewhere; that is to say, by resting and elevating the affected part, and thereby diminishing as far as

possible the hydrostatic pressure in the distended vessels.

The best results are obtained by putting the patient to bed on an inclined plane with feet elevated, by restricting the amount of food and fluid, and by gentle purgation and absolute rest. Washing out the bladder with some bland substance, such as boric acid, appears to be the best form of treatment; if there is an admixture of blood, styptics may be added, as follows:

Paez writes of the treatment by hetrazan and finds that the microfilaria disappear from the blood and urine. Hetrazan is given in doses of 1 mgm. per kg. three times daily for seven days. After an interval a second course is taken of 150 mgm. daily for twelve days for a total of 1.75 grm.

Golden and O'Connor found improvement after X-ray treatment to the

kidney region in seven cases.

Chylous dropsy of the tunica vaginalis, and of the peritoneum; chylous diarrhea.—Chylous dropsy of the tunica vaginalis is not unusual in the tropics. A fluctuating swelling which does not transmit light, and which is associated possibly with lymph scrotum, with varicose groin-glands, with chyluria, or with microfilariæ in the blood, would suggest this condition.

Treatment.—These chyloceles may be treated as ordinary hydroceles, either by aseptic incision or by injection. As a rule, the chylous fluid rapidly coagulates when withdrawn, but occasionally it does not, or it may be prevented by drawing the fluid off into a solution of potassium citrate.

If a minute portion of absorbent cotton is dipped into the receptacle, it will slowly fall to the bottom of the fluid. If the cotton is now picked up and placed under a low-power microscope, it will be found that every fibre is beset with multitudes of wriggling microfilariæ entangled by their sheaths, the preparation suggesting the snake-beset Gorgon head.

Filarial orchitis with effusion into the tunica vaginalis, according to Maitland, is best treated by incision of the tunica vaginalis, turning out any clot that may be found in the sac, and stuffing the latter with iodoform gauze.

Chylous dropsy of the peritoneum and chylous diarrhœa of filarial origin are very rare.

Filarial orchitis, endemic funiculitis, and hydrocele.—The fever attending filarial orchitis—which is usually associated with lymphangitis of the spermatic cord—has been described as "endemic funiculitis," but it is undoubtedly of filarial origin. It may be attended with inflammation of the scrotum, and, like ordinary elephantoid fever, resemble very closely a malarial attack. In these cases the Editor originally demonstrated large numbers of microfilariæ in the tunica vaginalis at the commencement of each attack. The aspirated fluid is cloudy, contains a number of polymorphonuclear cells, and occasionally erythrocytes, with microfilariæ. The epididymis is enlarged and nodular. In sections, dead and calcified filariæ blocking the vasa efferentia cause extensive fibrotic changes, and it is possible that sterility may be a direct result of this infestation.

The primary lesion is a sterile inflammatory reaction about a dead worm in a lymphatic vessel. With the vessel occluded, an obliterative lymphangitis results, which in turn causes dilatation, hypertrophy and varicosity with peripheral lymph stasis. The lymphatics of the testis are specially vulnerable to such lesions as they are long, without collaterals, and drain against gravity. Lymph stasis in the testicle is shown by definite clinical signs in the cord, epididymis and testis.

Recurrent attacks of filarial orchitis lead sooner or later to hydrocele. This condition very commonly accompanies elephantiasis of the scrotum, especially among Polynesians. The walls of the sac are thickened and contain calcified remains of adult filariæ; the hydrocele fluid is clear, straw-coloured, and usually contains microfilariæ, though it does not seem to be a medium particularly favourable to them. Filarial infiltrations of the cords vary in size, form, and number. There may be one single nodule as small as a pea, or a number may be strung to thickened lymphatic vessels. Sometimes lymphatic obstruction affects the vessels so as to cause lymphangiectasis and lymphatic varicoceles; it may, however, cause cystic dilatation, or "lymphocele." The spermatic veins are often the seat of chronic thrombo-phlebitis.

Treatment.—The living membranes of the sac can be obliterated by injection or open operation. Injection treatment is suitable for the small, flaccid, thin-walled sacs, but operation is better for the others.

These conditions can best be treated by surgical means, though Earle claims that sulphapyridine in doses of 4 grm. daily cuts short attacks of orchitis and funiculitis.

Differential diagnosis has to be made from encysted hydrocele, lipoma, spermatocele, vaginal hydrocele, syphilitic orchitis, gonorrheal epididymitis, strangulated hernia, and suppuration of the spermatic cord. Non-filarial epidemic funiculitis has been described by Power (1946) in British troops in Ceylon. This is localized induration of the spermatic cord which is due to a thrombosis in the veins. Specimens removed show a twisted mass of veins representing the whole pampiniform plexus, sometimes the thrombi break down into pus containing streptococci. It is accompanied by redness and cedema of the skin, fullness of the cord and sometimes by a small hydrocele. At first there is pain in the groin shifting to the testes with redness of the scrotal skin.

Septicamia. Septicamia due to Streptococcus hamolyticus is not infrequent in subjects infected with W. bancrofti. The parent worm in the lymphatic system damages the liming of the vessels, and thus prepares the ground for pyogenic organisms which invade the lymph-stream. In damaged lymphatic tissue streptococci find a favourable medium, enter the blood-stream, and septicamia ensues.

Filarial synovitis.—Acute synovitis of the knee-joint is one of the filarial diseases, and its concurrence with filarial invasion is too common to be accidental; fibrotic ankylosis often results. Where the hip-joint is affected, removal of the inflamed iliac glands draining the area sometimes relieves the condition.

In severe cases synovitis may proceed to pus-formation, often with a fatal result. Surgical intervention is therefore indicated.

ELEPHANTIASIS

In certain districts in Cochin about 5 per cent. of the population, in Samoa and Tahiti about every second individual, and in Huahine seventenths of the adult male population, are affected by this disease. In the Ellice Islands, out of a total population of 3,484, 90 per cent. are affected. In many other tropical and subtropical countries elephantiasis, if not so common as in those mentioned, is, nevertheless, very prevalent.

The pathology of the disease is considered on p. 748.

Parts affected.—In 95 per cent. of the cases the lower extremities—either one or both—alone, or in combination with the scrotum or arms, are the seat of the disease. The foot and ankle only, or the foot and leg, or the foot, leg, and thigh may each or all be involved. The arms are more rarely attacked, though in W. Pacific this is comparatively common; out of 47 cases the arms alone were affected in 10, arms and legs in 6 cases. Still more rarely involved are the mammæ, vulva and circumscribed portions of the integuments of the limbs or trunk.

In any of these situations, the disease commences with a rapidly evolved lymphangitis, dermatitis and cellulitis, accompanied by elephantoid fever. O'Connor demonstrated that the attacks arise from painful areas known as "focal spots," and in a large proportion of cases it has been possible to demonstrate dead and calcifying filariæ by X-ray examination.

The lymphatic glands draining the affected area are generally enlarged. There is no distinct line of demarcation between healthy and diseased skin. The implicated integuments are hard, dense, pit but slightly, if at all, on pressure, and cannot be pinched up or freely glided over the deeper parts.

On cutting into the swelling, the derma is found to be dense, fibrous and enormously hypertrophied. The subjacent connective tissue is increased in bulk, having, especially in the scrotum, a yellowish, blubbery appearance from lymphous infiltration. A large quantity of fluid wells out on division of such tissues.

Elephantiasis of the legs. (Fig. 169).—Elephantiasis of the lower extremities is usually, though by no means always, confined to below

the knee. The swelling may attain enormous dimensions and involve the entire extremity, the leg or legs attaining a circumference, in aggravated cases, of several feet.

Treatment.-Golden and O'Connor (1934) reported on irradiation by X-rays of lymphangitis and adenitis. At first, merely focal spots were so treated, but later the entire leg. Out of fifteen cases four had no further attacks. The patient should be encouraged to persevere with elastic bandaging, massage, and elevation of the limb. Swellings in the early stages may to some extent be controlled by elastic bandages or stockings. The latter. which should be made to fit the legs accurately, should be of some elastic andwashable material, such as stockinette. Such a stocking (Fig. 170A) should embrace the dorsum of the foot and should accurately fit the leg to reach above the knee. Difficulty is generally experienced with the



Fig. 169.—Elephantiasis of legs; scrotum and right arm also affected. (Photograph: Dr. Turner, Samoa.)

upper margin, which extends to the thigh, as it is apt to constrict or nip the limb at this point. To obviate the pressure and discomfort of tight-fitting stockings, and to accommodate the fluctuations in the size of the limb which necessarily take place, these stockings may be made to lace up at the sides (Fig. 170B). A spiral elastic stocking, made by Down Bros. on Dickson Wright's model, which can be accurately fitted to the

leg and which is comfortable, airy and effective, can be recommended. The technique varies according to whether the leg is cylindrical, cedematous or lobulated. In the cedematous form bandaging methods should be employed. Knott is an advocate of prolonged and firm bandaging, which effects a gradual removal of the lymphædema, during which time the patient obtains symptomatic relief and avoids further recurrent attacks of lymphangitis; the bandages should not be removed when an attack of lymphangitis is imminent, but the foot of the bed should be elevated. A "bandage boot" is used, consisting of a 6-inch bandage of heavy Turkish towelling, which covers the limb from behind the heads of the metatarsals to the heads of the tibia and fibula, cemented to a covering crêpe bandage by dextrin-syrup applied along the tibia, the whole being supported by narrow lateral strips.

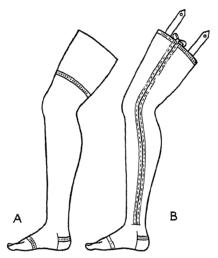


Fig. 170.—A, Plain web-elastic stocking, with foot-piece, for slight degrees of elephantiasis of leg. B, Laced form of elastic stocking, with suspenders, adjustable so as to avoid pinching. (A, James Woolley & Sons, Manchester; B, Hospitals & General Contract Co.)

Operative measures.—Sometimes in advanced cases good results follow excision of redundant masses of skin. A curved incision should be made from the head of the tibia to the ankle joint; two further incisions at upper and lower ends make a Y shaped cut. The skin is separated on both sides laterally as far as possible. The elephantoid tissues thus exposed are now incised along the whole margin as far as the periosteum and a similar incision is made parallel to this down to the muscle fascia. This separation is repeated in ring-like strips down the leg until none of the proliferated tissue remains except part of it behind the calf.

Junge's methods are as follows:—To restore the flow of lymph, about twenty-five windows are cut in the muscle fasciæ over the whole of the leg, each bigger than a postage stamp, but none is cut over the tibia. Into each of these windows a double silk thread is inserted by passing the needle deep through the muscle. The hanging ends are arranged like candle-wicks to suck out lymph over the widest possible area of the leg. The skin flaps are then replaced.

Various other operative measures have been proposed, though none is entirely satisfactory. Lanz's operation aims at deep lymphatic drainage. A longitudinal

incision is made through the fascia lata down to the femur, the periosteum of which is stripped and the bone trephined in several places; strips of fascia are then inserted into the openings thus made.

Kondoleon's operation consists also in free incision of the fascia lata and removal of large sections of the aponeurosis, which assists in the anastomosis

of lymph channels and veins.

Auchincloss's operation is intended to lighten elephantoid legs, and also to remove those tender focal spots whence the inflammatory lesions of filarial fever arise and to excise calcified worms. It consists of two incisions marking out a vertical strip of skin. From its ends V-shaped incisions are made diverging upwards at the upper end and downwards at the lower. An almost dangerously wide amount of skin is undermined, with considerable care, just deep to the corium.

Medical treatment.—Bowesman has advocated a method of treatment of filaria elephantiasis by intra-arterial injection of glycerine. This depends upon the inherent attraction of glycerine for water so that, when placed in contact with living tissues, it causes a movement of the fluid from the tissue spaces towards the vessels or the region in which the glycerine is placed. Injections of 10 per cent. sterile glycerine in water are given at intervals not less than one week apart,

into the femoral artery, the optimum dose being 2-3 ml. of a 10 per cent. solution. In making the injection the needle is introduced into the artery and then the syringe containing the solution is attached. No pain or discomfort is noticed if the injection is made slowly. The effect of intravenous medication is not so marked as intra-arterial. The decrease in size of the limb appears to be fairly permanent.

Elephantiasis of the scrotum.—Elephantiasis of the scrotum or "scrotal tumour" as it is sometimes called, may attain an enormous size: 10, 15, 20 lb. are common weights for these tumours, and 40 or 50 lb. is by no means uncommon. The largest recorded was 224 lb.

Anatomical characters.—These tumours consist of two portions (Fig. 171): first, a dense rind of hypertrophied skin with wart-like thickenings (A, e), thickest towards the lower part and gradually thinning out as it merges above into the sound skin of the pubes, perineum and thighs; secondly, enclosed in this rind, a mass of lax, blubbery, dropsical, areolar tissue in which testes, cords and penis are embedded. The shape of the tumour is

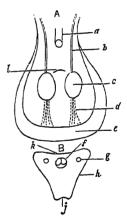


Fig. 171.—Diagram of anatomy of elephantiasis of scrotum. (For references, see text.)

more or less pyriform. The upper part, or neck, on transverse section (B) is triangular, the base (B, k) of the triangle being in front, the apex (B, j)—usually somewhat bifid from dragging on the gluteal folds—towards the anus, the sides (B, h) towards the thighs. In the latter situation the skin, though usually more or less diseased, is, from pressure, softer and thinner than elsewhere, tempting the surgeon to utilize it for the formation of flaps—not always a wise proceeding. The penis (A, a, B, f) always lies in the upper and fore part of the neck of the mass; it is firmly attached to the pubes by the suspensory ligament. The sheath of the penis is sometimes especially hypertrophied, in some cases standing out as a sort of twisted ram's-horn-like projection on the anterior surface of the

tumour; this, however, is unusual. Generally the sheath of the penis is incorporated in the scrotal mass, the prepuce being dragged on and inverted so as to form a long channel leading to the glans penis and opening (A, l) half-way down, or even lower, on the face of the tumour. The testes (A, c), buried in the central blubbery tissue, usually lie towards the back of the tumour, one on each side—in large tumours generally nearer the lower than the upper part. They are more or less firmly attached to the underpart of the scrotum by the hypertrophied remains of the gubernaculum testis (A, d)—a feature to be specially borne in mind by the surgeon. As a rule, both testes carry large hydroceles with thickened tunicæ vaginales. The spermatic cords also (A, b; B, g) are thickened and greatly elongated. In spite of the grave alterations in the tissues the functions of the testes remain unimpaired.

The arteries which supply these enormous growths are of considerable size; the veins, too, are very large and, as they permit regurgitation of blood from the trunk, are apt to bleed freely.

Treatment before operation.—If the tumour is of considerable size the patient should keep his bed for at least a week before operation, the mass being suspended so as to drain it of fluid and blood. It is thus rendered lax, and the operator can ascertain by palpation the position of the testes and of any hernia—a not very unusual complication. The possibility of undescended testes should not be overlooked. The choice of anæsthetic is important: it should be spinal when possible, reinforced with gas and oxygen. The patient should not be kept long in bed before the operation, for when the mass is supported, the fluid drains upwards and invades the tissues to be used for flaps, and the palpable edge of the elephantoid skin is obscured.

Operation.—The patient should be placed in the lithotomy position. The scrotum should be drawn down as far as possible and elastic webbing applied over the mass so as to expel the blood; a stout rubber cord is wound round the neck of the tumour, over the pelvis, and firmly secured. A vertical incision is made, commencing in the middle of the symphysis pubis and extending as far as the aperture leading to the penis. The penis is exposed, separated and the penal artery ligatured. It should be borne in mind that the prepuce and skin of the sheath of the penis have been pulled down over the glans, and form a skin-lined tube from the glands to an opening on the front of the tumour, and, while the skin of the prepuce and the sheath and even the frænum may be elephantoid, the skin of the glans is normal. At this point, a sound is passed, and left in to prevent subsequent injury to the urethra. The vertical incision is now continued round the scrotum right round to the back of the perineum, and the scrotum is thus divided into two halves. The testicles and cords are now separated from the blubbery mass, the hypertrophied gubernacula being divided, surrounded with gauze and placed on one side. At the base of each half of the scrotum clamps are fixed, care being taken that these clamps are well to the proximal side of all diseased tissue. Each half of the scrotum is then cut away, distal to the clamps, and through healthy tissue. Every visible blood-vessel is secured and tied and the clamps very gradually loosened. The skin in the upper and inner aspects of the thigh is undermined as much as necessary and brought together over the testicles. Thiersch skin-grafts may be applied to the penis, and give good cosmetic and functional results, and, if done at the time of the operation, will take in 100 per cent. of cases. It is a good procedure to tie in a catheter until healing has taken place.

Complications which may ensue are severe hæmorrhage, and injury to spermatic cords, urethra or rectum. Postoperative retention of urine is often very trouble-some. Stricture of the urethra and the supervention of elephantiasis of a

previously unaffected leg have also been recorded.

The mortality from these formidable-looking operations, if they are carefully done, is small, and need not exceed 5 per cent.

Knott insisted that the most important factor is the position of the patient on the operating table. If the patient is placed on a horizontal table with his legs over the sides supported by chairs, the mass can be rolled to the opposite side, and this does away with the need for a rubber tourniquet.

Early cases of elephantiasis of the scrotum, still subject to attacks of fever with lymphangitis and cellulitis which involves the skin of the penis and scrotum,



Fig. 172.—Elephantiasis of right arm and hand in a Fijian.

require to be handled in a different manner. In these cases enough skin should be saved to cover the testes, and the more skin taken, the less likelihood there is of a recurrence. Modern surgeons are concerned with restoration of the penis. Some take skin from the mons veneris to cover it, others from the sides of the scrotum, but this is often diseased. The scrotal suture should be as far as possible from the anus. The suture takes the form of a double cross, and a glass or rubber drain is inserted.

Elephantiasis of the arms.—This is comparatively rare except in the Pacific (W. pacifica). Allowing for the gravitation differences between the upper and lower extremities, the symptoms and pathology of

elephantiasis of the arms are the same as those of elephantiasis of the legs. Beyond the judicious employment of massage and elastic bandaging, little can be done in treatment. (Fig. 172.)

Elephantiasis of the vulva and mammæ.—Elephantiasis of the vulva and mammæ is still rarer. Where growth has become inconveniently large, the diseased tissues should be removed. Instances are on record in which the integuments of the mammæ have become so thickened, heavy, and elongated that the organ has descended to the pubes, and even to the knees. One such tumour weighed 21 lb. after removal. Tumours of the labia or of the clitoris, similarly, may attain a great size—8 or 10 lb., or even more.

Elephantiasis of limited skin areas.—Corney stated that pedunculated elephantoid tumours, springing from the groin or from the anterior surface of the thigh, were not uncommon in Fiji. One such tumour which he removed weighed 20 lb. Daniels saw, both in Fij and in Demerara, several cases of this description.

Filariasis and elephantiasis due to Wuchereria malayi.—It is claimed that the clinical manifestations produced by this species differ in some respects from that produced by Wuchereria bancrofti, a fact that was recognized by Poynton and Hodgkin. W. malayi is endemic in Malaya, Southern India, S. China and Ceylon, in the low-lying riverine areas, where the rivers run into the sea. The microfilaria-rate in the natives living in the vicinity of swamps is 9-3 per cent., which is about the same as the elephantiasis rate; as with W. bancrofti, the liability to infection increases with age.

Adenitis is the earliest detectable lesion; inflammation of the groinglands is frequently seen in children. Lymphangitis is also a familiar phenomenon and has a definite periodic character. Elephantiasis due to Wuchereria malayi is low-grade, invariably confined to the legs, and is usually unilateral. The surface of the skin is usually smooth. There appears to be great variability in the rate at which elephantoid lesions are produced. In highly infected areas it is seen in comparatively young people, especially in males, though it is typically a disease of adult life. Microfilariæ are, as a rule, found only in 5 per cent. of cases. The absence of chyluria and the rarity of scrotal swellings in association with W. malayi has been noted.

Medicinal treatment of filariasis. — Culbertson and Rose, having demonstrated that the antimonials—neostibosan and neostam—injected into cotton rats (Sigmodon hispidus) will kill the adult filariæ (Litomosoides carinii) in the pleural cavities, have applied this knowledge to human filarial infections. The first results, obtained in Porto Rico, were rather inconclusive. The patients received 9–12 grm. of the drug over a period of 25 to 40 days. In some two daily injections were given and in some cases the course was repeated after nine months' interval. Followed up for two years 15 out of 20 became free of circulating microfilariæ. In other cases the antimony treatment appeared to have had no effect on the numbers or behaviour of the microfilariæ.

Sodium thiacetarsamide (arsenamide)—Otto and Maren, 1950; Hawkins, 1951—is administered intravenously for 15 daily doses, which appears

sufficient to completely eliminate microfilariæ in patients suffering from the non-periodic type (W. pacifica) (Otto and others, 1953). After injection there is an actual increase in the number of microfilariæ for it acts on the uterus of the adult female causing a sudden discharge of embryos. In some of the patients treated with this drug in 2 per cent. solution, in doses of 1.0 mgm./kg. for 15 days, microfilariæ were absent from the peripheral blood after an interval of two years, indicating the probable death of the adult worm or worms.

Hetrazan (or Banocide), a piperazine compound, introduced by Welch, Peters and colleagues in 1947, is issued in the form of the hydrochloride and the citrate. It was first tried out on the filaria of the cotton rat. Santiago-Stevenson and others then treated 26 patients with microfilaria bancrofti in Porto Rico in tablet by mouth of 0.5–2 mgm. per kg. three times daily in a period lasting from three to twenty-two days. It was found that within a very short time from administration these small worms disappeared from the blood stream, but the final results on the adult worms could not be ascertained. Hawking, Sewell and Thurston (1950) have tested out antifilarial action on Litomosoides carinii of the cotton rat and Dirofilaria immitis of the dog. A marked but irregular reduction in numbers took place, but even with doses approaching the maximum tolerated all microfilariæ did not disappear from the blood. The adult worms were little affected.

Hawking demonstrated that hetrazan and its metabolic products exert no direct action on the microfilariæ, but it appears to modify them in some way so that they are engulfed by pagocytes of the endothelial system and thereby removed from the circulation. In shut off cavities such as hydroceles, the microfilariæ are not affected. When injected intravenously microfilariæ disappear almost instantaneously.

Further reports deal with a large series of 74, including 54 males and 20 females, studied in Porto Rico, as well as in British Guiana, the Virgin Islands and the Gambia. In the majority, regardless of dosage, a marked reduction in the numbers of microfilariæ resulted within the space of 2-4 days after the first dose. These reductions are sustained throughout the period of treatment, but a few recurrences have been observed and approximately one-third had negative counts from 3-6 months after cessation of treatment. Side reactions included headache, nausea, vomiting, and sometimes, skin rashes. In St. Croix, Virgin Islands, hetrazan has been made available to every inhabitant. There the incidence of W. bancrofti is about 20 per cent. of the population. The dosages used for 98 cases were:—

- 11 cases once daily for 5 days = 90.6 per cent reduction.
- 39 cases thrice daily for 3 days = 92.4 per cent. reduction.
- 19 cases thrice daily for 5 days = 90.8 per cent. reduction.
- 29 cases thrice daily for 7 days = 96.9 per cent. reduction.

This would indicate increasing reduction with increasing dosage and that the effect lasts about four weeks.

Hewitt and colleagues in a second report on mass treatment found that thrice daily dosage for seven days gave the best results for the whole

population. In groups under control the reduction of microfilariæ in the blood was about 82 per cent. and it is claimed that hetrazan provides the most practicable and convenient method for reducing the reservoir of microfilariæ. In Georgetown, British Guiana, 216 patients were treated with doses from 0.2-2.6 mgm. per kg., the total dose being 13-193 mgm. per kg. At the end of treatment 95.8 per cent. of 216 were negative for microfilariæ; after six months 71 per cent. and after ten 65 per cent. Total doses of less than 50 mgm. per kg. were not so effective in removing microfilariæ as the larger doses, but otherwise there did not seem to be relation between dose and effect. In Uganda no significant difference has been noted in cases taking less than 50 or more than 100 mgm. per kg., and the reduction in the numbers of microfilariæ in the capillary blood is 90 per cent. or over. To avoid any irritating effect on the stomach the drug is given as the powdered citrate which is soluble and pleasant to take. The accepted doses for W. bancrofti now is 6 mgm. per kg. (or 38 mgm. per stone of 14 lbs.) daily in divided doses of three after meals. Thus a patient weighing 12 st. should receive a total of 450 mgm. daily, in three doses of 150 mgm. each for 2-3 weeks in mild, and 3-4 weeks in acute cases.

The toxic effects are not serious but consist of anorexia, nausea, drowsiness, headache, and vomiting. Allergic reactions have been reported, especially in the Pacific form. When doses of 12 mgm. hetrazan citrate per kg. of the drug, given every 12 hours, the level of hetrazan base in the blood is about 3 μ grm. per ml. The excretion in the urine is at the rate of 15 mgm. base per hour.

The treatment of W. malayi with hetrazan is the same as for W. bancrofti but the resulting allergic reactions are said to be more severe (Hawking, 1950).

Prophylaxis of filarial disease.—The prevention of filarial disease resolves itself into anti-mosquito measures and protection from mosquito-bite. Unprotected wells, tanks, cesspits or stagnant pools must not be permitted in the neighbourhood of dwelling-houses. All vessels used for storing water should be emptied at least once a week. The mosquito-net is indispensible in filarial as well as in malarial countries. In the Pacific Islands, especially in the Gilbert and Ellice group, considerable reduction of filarial incidence has taken place following O'Connor's recommendation to cut down the thick undergrowth, thus giving passage to the Trade Winds which blow away the mosquitoes (Aedes scutellaris polynesiensis). Burning empty coconut shells and filling up holes and cavities in the trunks of the coconut trees has been beneficial, as it destroys breeding places.

Active measures are now being undertaken in Tahiti and Fiji and other Pacific islands to combat filariasis, by spraying with DDT, bush clearing and prophylactic administration of hetrazan. The training of special anti-filarial teams, as in Fiji under D. W. Amos, is a practical method of great importance. In the island of St. Croix, West Indies, the U.S. Public Health Service introduced residual insecticide methods against Culex fatigans and Aedes ægypti. The best method was found to be DDT-Xylene-Triton emulsion (85 per cent. DDT-Xylene concentrate with Triton X-100 diluted with water to form a 5 per cent. spray). In all

11,078 houses were sprayed each on four occasions. The result was a 50 per cent. reduction of C. fatigans whilst A. ægypti seemed to have

disappeared (Kohler, Brown, and Williams).

Mass treatment with herrazan is now being instituted in the Virgin Islands, Tahiti and elsewhere with the idea of banishing microfilariæ from the peripheral blood, thus breaking the chain and rendering mosquito transmission impossible. The most detailed campaign so far conducted is by McGregor, Hawking and Dean Smith (1952) in the Gambia. Hetrazan citrate was given in 25 mgm. per kg. for five days. Of 154 infected persons 64 per cent. had their blood free from microfilariæ for 10 months, and in the remainder the parasitæmia was substantially reduced. These doses were not well tolerated. Beye, Kessel and colleagues (1953), in mass treatment in Tahiti, also succeeded in reducing the microfilarial density after two hetrazan courses of seven days each, but after two years the effect was not so striking, though the "larval index" in Aëdes scutellaris mosquitoes was reduced to one tenth.

In W. bancrofti filariasis, in which the periodicity is nocturnal, and where night-biting mosquitoes, such as Culex fatigans and Anopheles, are concerned in transmission, the disease should be treated as a house-infection by sanitary measures and DDT sprays which in this respect

have been eminently successful.

Iyengar (1937) conducted a successful campaign against the intermediary mosquito of Wuchereria malayi—Mansonioides annulifera, and the water lettuce Pistia stratiotes, to which the larvæ become attached, and succeeded in clearing this plant from North Travancore, with the consequent elimination of filariasis from that area. The species of Mansonioides which act as vectors in Malaya flourish in association with the roots of swamp trees. The methods adopted in Travancore, therefore, cannot be applied to Malaya. (See pp. 994–995.)

The subjects of filariasis should be regarded as dangers to themselves and to the community, and be compelled to sleep under mosquito-nets.

II. FILARIASIS DUE TO LOA LOA (LOAIASIS)

History and geographical distribution.—The embryonic form (microfilaria diurna), which closely resembles microfilaria bancrofti, was described by Manson in 1891; the patient from whom the specimen of blood was derived had formerly had an adult *Loa loa* in his eye. Later, association was established between *L. loa* and the disease known as Calabar swellings, and also between that disease and microfilaria diurna.

Loa loa is widely distributed in West Africa from 8° N. to 5° S. of the equator from the Gulf of Guinea eastwards to the Great Lakes. It is especially common in the Cameroons and on the Ogowé River; its distribution is, however, mainly confined to the coastal plains, and follows the course of the Congo and its tributaries to a point about 1,500 miles from its mouth (Map VIII). This parasite is also found in the Southern Sudan between the Bahr el Ghazal and the Belgian Congo between latitudes 4° and 6° N. and longitudes 27° and 31° E.

Ætiology.—A description of the adult Loa loa is given in the Appendix, p. 996. Here it suffices to say that it is 30 mm. or more in length, the female

 γ

Fig. 173.—Loa loa. Nat. size.

being, as a rule, considerably longer than her partner (Fig. 172). The cuticle is embossed with numerous characteristic protuberances.

Structure of the embryonic form.—Microfilaria loa (= diurna) is very similar in size (298 μ by 7.5 μ) and structure to microfilaria bancrofti. Like the latter, it is enclosed within a "sheath," its tail is pointed, and it has similar V- and tailspots. (Fig. 152, 2, p. 736.)

The periodicity is the exact reverse of that of microfilaria bancrofti, for the embryos appear in

large numbers in the peripheral blood during the daytime and disappear at night. The periodicity is, in fact, diurnal (Chart 29).

The respective periodicities are very characteristic—more so, apparently, in microfilaria loa than in microfilaria bancrofti; for, whereas by inverting the sleeping habits of a subject of W. bancrofti infection it is easy to invert or disturb the periodicity of the microfilariæ, this has not been done so easily with microfilaria loa, although several experiments have been made. It does, however, take place gradually, as for instance when the patient travels round the world

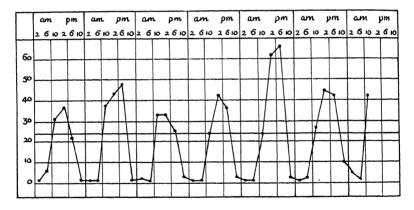


Chart 29.—Diurnal periodicity of microfilaria loa (mf. diurna).

The numbers in the first column are those of the microfilarke per 16 ml. of blood.

(Külz, 1914). In Americans who have been infected in West Africa, the microfilariæ maintain their periodicity on their return home. A series of important observations on the mechanism of periodicity were made by Gönnert, who was transfused with blood from a patient heavily infected with L. loa and D. perstans, whose blood contained 1,640,000 of the former and 112,000 of the latter per 160 ml. Subsequently, microfilariæ loa were demonstrated in the recipient's blood and maintained a strict diurnal periodicity for three days. Most of the microfilariæ perstans disappeared from the blood within the first few days, but some persisted for at least three years. Somewhat similar results were obtained with microfilaria bancrofti by Knott and Hawking.

Life-history.—In early editions of this work Manson called attention to the mangrove fly, Chrysops dimidiata (Fig. 378, p. 1050), as a possible intermediary, on account of its diurnal and blood-sucking habits and local distribution. This conjecture Leiper, and later Kleine and Connal, have ascertained to be well-founded. Development takes place in the thoracic muscles and fat-body of C. dimidiata and C. silacea, and in the Southern Sudan probably in C. distinctipennis. C. longicornis does not transmit.

After the larva has entered the human body, development seems to be very slow, and probably full maturity is not attained until a year or longer. In Johnstone's case (1947) the evolution from larval to adult stage was exactly one year. In many cases the parasite does not show itself until three, four, or four and a half years after the patient has left the endemic area. In one case it was extracted from the eye thirteen years after the patient had left Africa; in another, the worm or worms appeared at irregular intervals during fifteen years, and the Editor has records of finding live microfilariæ in the blood for a period of seventeen years. Manifestly it is long-lived. An interesting and suggestive evidence of slow development is that, while the immature active worm is often seen in children, the embryonic form in the blood is found as a rule only in adults, it may be as long as seven years from the time of the original infection.

This slow development of L. loa seems to account for the very frequent failure to find the microfilariæ in the blood in cases from which mature parasites have been extracted, a circumstance which has been brought forward as an argument against the theory that the diurnal microfilaria is really the offspring of L. loa.

As yet it is impossible to estimate accurately the number of adult worms present in any given infection, although in advanced cases some idea might be obtained from the number of microfilariæ in the peripheral blood. As a rule, it is safe to conclude that the particular loa that may show itself about the eye or elsewhere is only one of many. Thus, in 1903, Brumpt, at the autopsy of a negro whose blood contained microfilariæ, found in the tissues of the heart five adult worms. Four of these were cretified, but the fifth was alive and contained embryos similar to those in the blood.

Pathology.—L. loa, during the period of its growth and development in man, makes frequent excursions through the subdermal connective tissues. It has been noticed very often beneath the skin of the fingers, and it has been excised from under the skin of the back, from above the sternum, from the left breast, the lingual frænum, the loose skin of the penis, the eyelids, the conjunctiva, the anterior chamber of the eye, and also the scalp. The parts most frequently mentioned are the eyes, and, although the worm may attract more attention in this situation, it does seem as though it had a decided predilection for the eye and its neighbourhood (Fig. 174). A patient of Manson's once stated that the average rate at which a loa travelled was about an inch in two minutes. Both he and others have observed that warmth, such as sitting before a fire, seems to attract them to the surface of the body. Chesterman on the Congo reported finding live adult worms in 10 per cent. of all cases operated upon for hernia and elephantiasis. Cretified worms, too, were frequently encountered. Whether alive or dead, this parasite evokes a high eosinophile response, and an increase to 30, 40, and even higher percentages, is common in Europeans who have resided in the endemic districts in Southern Nigeria, the Congo and Cameroons. Occasionally, as in one patient, who had manifested Calabar swellings over a period of seven years, all the

PARASITES OF THE LYMPHATIC SYSTEM AND CONNECTIVE TISSUES

adult filariæ appeared to die out at the same time and were discharged in a calcified state from minute chronic abscesses which appeared on the hands, arms and legs.

Symptoms.—As a rule, the migrations of the parasite give rise to no



Fig. 174.—Loa loa in the eye. (After Fülleborn.)

serious inconvenience, but they may cause prickings, itching, creeping sensations, neuralgia and, occasionally, transient ædematous swellings (Calabar swellings) in various parts of the body. When the parasite appears under the conjunctiva it



Fig. 175.—Calabar swelling of right eye.

may cause a considerable amount of irritation and congestion; there may even be actual pain, associated with swelling and inability to use the eye and, perhaps, tunnefaction of the eyelids (Fig. 175). Should a loa wander into the rima glottidis, or the urethra, the consequences might be serious, and great pain is sometimes caused. Occasionally, too, as Chesterman recorded, the death of the parent worm may cause a localized abscess in the groin or axilla.

CALABAR SWELLINGS

Under this name Thompstone originally described certain fugitive swellings which are frequent in natives and Europeans alike in parts of tropical West Africa. The swellings are about the size of half a goose egg, painless, though somewhat hot, both objectively and subjectively, not pitting on pressure, and usually disappearing in about three days. They come suddenly and disappear gradually, and occur in any part of the body. One swelling occurs at a time, but recurs at irregular intervals and, perhaps, for many years after the patient has returned to Europe. In some instances the swellings seem to be due to rubbing provoked by the irritation accompanying the presence of a loa just under the skin; in other instances they develop spontaneously. In Johnstone's own case a localized Calabar swelling appeared round the worm as it lay coiled up in the outer aspect of the upper eyelid. In the hand or forearm they may give rise to a sensation of powerlessness and soreness, as if the part had

received a blow. They never suppurate (Fig. 176). The effects of temperature upon these swellings is important. During the hot summer months they are most frequent: in the cold weather distinctly uncommon.

Although in a large proportion of cases, L. loa embryos cannot be found, in a number of others, either the parent worm has shown itself in the eye, or its microfilariæ have been detected in the blood. This discovery, together with the geographical endemicity of these swellings and their clinical characters, makes it practically certain that they are produced by L. loa. Manson believed that the swellings might be caused by the emission of her larvæ by a parent loa into the connective tissue, but it was proved by Fülleborn that they represent an allergic reaction on the part of the tissues in response to filarial toxins, and so can be reproduced by injections of extracts of the adult filariæ.

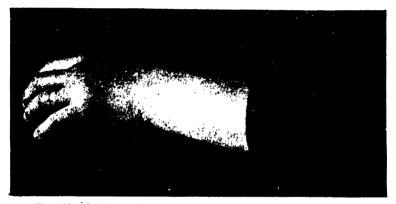


Fig. 176.—Calabar swelling on dorsum of hand in a European lady from the Congo.

The recurrence of Calabar swellings on the arm or leg appears to give rise to induration of the fascia and connective tissue round the tendon-sheaths. In two cases the Editor observed permanent circular cyst-like swellings which may cause pain on muscular movement. Apparently, they are attached to the tendon-sheaths and muscular aponeuroses. Solid ædema of one leg persisting for six weeks has been observed in a European from West Africa who had been infected for a number of years; hydroceles also have been recorded (Fig. 177).

Urticaria and dermatitis of a particularly irritating form with pruritus are sometimes found in filaria cases. The dermatitis is analogous to that found in onchocerciasis. As, in infections with W. bancrofti, multiple intramuscular abscesses, due to secondary invasion by staphylococci or streptococci, and even infections of the hip-joint, may sometimes be found in association with Loa loa.

Diagnosis.—The microfilariæ can be demonstrated in the blood, or the high eosinophilia (30-60 per cent.) suggests this parasite. Confirmatory evidence can be obtained by the intradermal or complement-fixation tests (p. 750). An antigen is prepared from the filariæ of the South

American ostrich (Contortospiculum rheæ), from the filaria of the cotton rat (Litomosoides carinii) or Dirofilaria immitis of the dog.



Fig. 177.—Hydrocele and solid ædema of right leg in L. loa infection from West Africa.

After washing and drying the worms are triturated and a 1 per cent. emulsion of the powder is made in 0.5 per cent. carbol saline. After centrifugation the supernatant fluid is used as an intradermal test of 0.1 ml. and gives good results. These reactions are generally more marked and reliable than in W. bancrofti infections: it must be emphasized that a diagnosis of L. loa has often to be made by such means, when no microfilariæ are present, for they may not appear in the peripheral blood for several years after the original infection.

Treatment. — Calabar swellings are notoriously difficult to treat effectively. The irritation can best be allayed by evaporating lead lotion, or by heliobrom (dibromotannate of urea) in alcohol. Fairley employed a desensitization method with increasing strengths of Dirofilaria antigen, from 0.5 ml. of the extract in normal saline, grad-

ually increasing to 5 ml. or more, and he had some success. De Choisy and others asserted that this infection may to some extent be controlled by injections of tartar emetic; and that in some cases Calabar swellings can be treated by intravenous anthiomaline injections every other day (3 ml. of a 6 per cent. solution), but hetrazan is more successful. John Lowe (1953) has suggested injection of A.C.T.H., which by depressing cell activity, suppresses the dermatitis.

Hetrazan.—Murgatroyd and Woodruff treated 17 Europeans in a series in which the infections had lasted from 1-24 years.

The dose was 2 mgm. per kg. three times daily lasting 10-21 days with total amounts of $1\cdot 2-10\cdot 5$ grm. Morbilliform and urticarial rashes ensued, alleviated only by benadryl and anthisan. In these serpigenous linear swellings due to adult worms appeared under the skin. The results were favourable and dead filaria were extracted from skin nodules. The filarial skin test remained positive, whilst in a small number the complement fixation test became negative.

Schneider (1950) treated a much larger series of 71 patients with daily doses for males of 0.4 grm. and 0.8 grm. for females for a similar period.

Allergic reactions were frequently encountered in some 70 per cent. These were pruritus, fugitive erythemata, Calabar swellings and creeping sensations beneath the skin. All these reactions responded satisfactorily to anti-histamine drugs.

Woodruff (1951) has shown by liver biopsy that, as in the case of filarial infections of laboratory animals with *Litomosoides carinii*, the microfilariæ quickly disappear from the blood and are destroyed in the liver after treatment with hetrazan.

III. HUMAN ONCHOCERCIASIS

History and geographical distribution.—Onchocerca volvulus was originally discovered by a German medical missionary in negroes of the Gold Coast. The contained parasite was named Filaria volvulus by Leuckart in 1898. Blanchard, in 1899, demonstrated the parasite lying in a lymphatic space in a tumour. It occurs sporadically throughout the whole of the Congo basin, but especially on the Oellé, Kibali and Itimbiri rivers. It has been observed in Nigeria (Best and Parsons), in the Cameroons, (Fülleborn), in Senegal and French Guinea (Clapier), in Uganda (Cook), in Togo, Dahomey and Ivory Coast, on the lower reaches of the Volta river on the Gold Coast (Hughes and Daly), in Kenya (Kakamega and Southern Kavirondo), in Tanganyika, in Nyasaland, and in the Southern Sudan (Bahr-el-Ghazal,—Bryant) (Map VIII).

In 1915 Robles described O. volvulus as being common in Guatemala. Caldéron (1920) defined the endemic zones as being in the departments of Sacatapéquez, Escuinthla, and Solola, at an altitude of 2,800-3,600 ft. It is suggested that the parasite was imported by negro slaves from Jamaica, though Brumpt classified the S. American worm as a distinct species-O. cœcutiens, "the blinding filaria"-mainly on account of its association with a curious punctate keratitis, minor distinctions in the morphology of the male parasite, predilection of the tumours for the head, and endemic zone of the disease at an altitude of 600-1,200 metres. De la Torre described onchocerciasis in Mexico, over 15,000 cases in the State of Chiapas and 5,000 in Oaxaca being known. On the other hand, Strong, Sandground, and Bequært (1934), in their monograph on onchocerciasis in Central America, demonstrated that O. volvulus and O. cœcutiens are morphologically identical. In Guatemala, onchocerciasis occurs endemically in those districts in which coffee is grown, from 2,800-3,000 ft., especially amongst the Indian population.

Ætiology.—The worms are white and filiform, tapering at both ends. They vary considerably in length, the female, as in all the filariæ, being much the longer (35–40 cm.). At least four males and two females are present in every tumour. The unsheathed embryos measure about 300 μ in length. Macfie and Corson found that in the Gold Coast natives microfilariæ are commonly encountered in sections of the skin, but some of the embryos, they believe, are referable to a new species, $Dipetalonema\ streptocerca\ (see\ p.\ 1001)$, distinguishable from those of $O.\ volvulus$. The presence of the microfilariæ of $O.\ volvulus$ in the skin is associated in some with a lichenoid condition.

Life-history.—Embryos, presumably those of O. volvulus, have been found in the peripheral circulation by Fülleborn, Simon, Ouzilleau, and Rodenwaldt; but usually the microfilariæ occur round the periphery of the tumours, and are ingested

by the jinja-fly (Simulium damnosum), in the thoracic muscles of which they undergo a development similar to that of W. bancrofti (Blacklock). In Kenya the species is S. neavei (Buckley), whilst in South America the insect intermediary hosts are Eusimulium avidum (metallicum), E. ochraceum and E. mooseri.

Gibbins and Lœwenthal showed that in Victoria Nyanza district of Uganda distribution of cutaneous onehocerciasis amongst the natives coincides with that

of Simulium damnosum.

Pathology and symptoms.—O. volvulus is found in peculiar subcutaneous fibrous tumours, the size of a pea to that of a pigeon's egg.

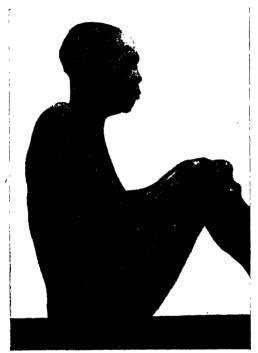


Fig. 178.—Onchocerciasis from the Congo. Typical nodules on knees, elbows and scalp. (Dr. C. C. Chesterman.)

The same patient may present one or several of these tumours (Fig. 178). The regions of the body most frequently affected are those in which the peripheral lymphatics converge. Thus, the tumours are usually found in the axilla, in the popliteal space, above the elbow, in the suboccipital region, and in the intercostal spaces. In their incipient stages they cause very considerable pain. Periodic recurrences of symptoms are attributable, according to native belief, to the lunar cycle, occurring almost every fifteen days. In the South American form the occipito-frontal and temporal regions are most usually affected. Strong found in Ste. Emilia, Guatemala, 54 per cent. of the inhabitants infected.

The tumours are situated on the head, usually the scalp, and measure 6-20 mm., rarely as much as 30 mm. They may cap the skull, and from them the adult worms may be obtained entire by digesting the tissues with papaya juice, or papaine, in 0.2 per cent. HCl. The tumours are never adherent to the surrounding structures and can be easily enucleated. They are formed of a dense mass of connective tissue, which enwraps the parasites and encloses small cyst-like

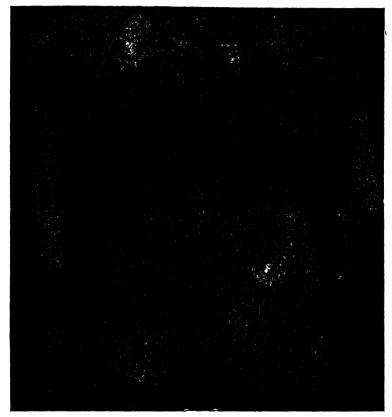


Fig. 179.—Lichenoid eruptions of onchocerciasis. (After Fülleborn.)

spaces filled with a greyish viscous substance consisting almost entirely of microfilariæ. The position of the adult worms within these tumours is very remarkable. The greater length of the coiled-up bodies of the females is embedded in the connective stroma; consequently they can only be extracted in fragments.

Becker has shown that free forms of adult worms commonly occur in the tissues, so that in many cases of onchocerciasis typical nodules are not found. Adult O. volvulus has been found in the course of operation for inguinal hernia and at Cæsarean section. Though they are most commonly found in adults of mature years, Strong saw volvulus tumours in a child of

two months, and found that they often give rise to neoplasms. Sometimes, however, especially in Europeans, the embryos may exist in large numbers in the skin without any palpable nodules.

Robles reported that tumours of the scalp and periosteum may produce epileptiform attacks in Colombia, due to perforation of the cranium. Erysipelatoid skin-rashes (known as "Erisepela de la costa") are common in the South American form.

Lymphatic enlargement of the scrotum, hydroceles and enlarged testes were noted by Dyce Sharp in patients infected with O. volvulus, while the embryos can be demonstrated in hydrocele fluid, as well as in ædematous lymphatic tissue. On the Congo, Ouzilleau and Chesterman described



Fig. 180.—Microphotograph of microfilaria of O. volvulus in subcutaneous tissue. Note absence of tissue reaction.

(Photograph by Dr. P. H. Martin.)

elephantiasis of the scrotum and legs in association with this parasite. As in W. bancrofti infections, localized abscess formation also occurs, and several dead female worms have been removed from abscesses. The elephantoid scrotum due to O. volvulus is convoluted like a brain, and the subcutaneous tissue is more solid and less adematous than that in elephantiasis attributed to W. bancrofti, while the embryos are found in the skin. Harris in Kenya noted a tendency to the formation of lipomata.

Van den Berghe recognizes several varieties of nodules—those with eggs; those with free microfilariæ; those with greenish, syrupy or caseous pus; cold abscesses full of pus and remains of worms and fibroid nodules

without eggs or microfilariæ.

Déjou (1939) described acute arthritis in onchocerciasis in French West Africa. Microfilariæ can be demonstrated in the synovial fluid obtained by joint puncture, which should be examined soon after

withdrawal. In these cases filarial nodules can be found in the cruroinguinal region, in the popliteal spaces, and on the costal margins.

Skin symptoms.—Dermatitis (xeroderma) or lizard skin (Rodhain and Dubois) is commonly associated with O. volvulus. The skin affection is described by some as lichenoid and is more easily visible on the back (Fig. 179). It is usually seen in South American cases, but shows up much better in Europeans than in dark-skinned natives. The skin is thickened as well as wrinkled, as Fülleborn described in German colonists from Mexico. This complication was termed lichen by Macfie and Corson and scleroderma by Ouzilleau in West Africa.

Recurrent inflammations of the skin of the face often result in enlargement of the pinna of the ear. Associated with this there is a definite dermatitis, with discoloured patches of skin on the neck and back, and xeroderma, especially of the elbows. The patient experiences terrible pruritus, especially at night. Quite commonly he suffers from photophobia and some aberrations of vision, and there is usually an eosinophilia of about 35 per cent.

Several onchocerca nodules can usually be found in the deep subcutaneous fascia, and when excised, the adult worms can be demonstrated, and living embryos also, by teasing a snippet from the surrounding skin in normal saline (Fig. 180).

Eye lesions.—In 1918 Pacheco Luna suggested that O. volvulus, in its migrations through the body, was responsible for a peculiar form of keratitis punctata commonly found in Guatemala. Caldéron claimed that

it produces lesions of the iris and cornea as well. Similar eye lesions were described amongst the Congo negroes by Hissette. Photophobia, xerosis and impaired vision result, or the pupil may become obliterated and complete blindness ensue (Fig. 181). In the acute stage eye lesions are associated with ervsipelas of the face and ear, and pyrexia. neuralgia chronic form is characterized by cedema of the face and a grevish pigmentation of the skin. Skin symptoms have periods of exacerbation every fifteen days. Further studies on the eyes were made by Strong and Sandground in Guatemala (1934). In Kenya



Fig. 181.—Ocular onchocerciasis from the Congo, showing punctate keratitis and lateral formation of pannus. (Hissette.)

Hawking, in the Kakamega district, found microfilariæ in the skin in 62 per cent. of a group with eye lesions or nodules. Eye lesions were present in 34 per cent. of those with microfilariæ, and in 23 per cent. of those without.

Silva found microfilariæ in the choroid and the posterior two-thirds of the cornea in sections of the eyes, and this was confirmed by demonstrations of living microfilariæ creeping on the corneal surface. They can be found.

too. in the anterior chamber and in the iris, as they are phototropic. Boase (1935), and also Mexican ophthalmologists, have identified them by the corneal microscope. Entropic vision of the embryos crossing the visual fields is said to be by no means uncommon. Several cases of blindness in Europeans from Kenya have been recorded in recent years and, in spite of all methods of treatment, pannus has steadily progressed. In none were palpable tumours demonstrable. It is to be noted that pannus was limited to the interpalpebral exposed surface of the eye and does not extend beneath the lids. In one corneal grafts were successful. Removal of operable tumours does not eradicate the disease, because new ones form. In Mexico City, where the disease cannot spread, microfilariæ can still be found in the skin as long as five years after widespread excision of nodules. Eve lesions are late manifestations of onchocerciasis, and are rarely seen in children. Van den Bergh suggests that the constriction of the head band, worn by West Africans may have a bearing upon the formation of symmetrical periauricular nodules.

Ridley (1945) was unable to detect microfilariæ by the slit-lamp in the cornea. He describes the eye in the early stages as white and free from vascular congestion, but with lacrymation and photophobia. Later, the cornea is thickened, pigmented and presents a marbled appearance. There are grey nummular opacities in the stroma, measuring 0.6 mm. in which bodies of dead microfilarize may be detected. Interstitial keratitis is found in the interpalpebral area. Later still, the corneal opacities fuse to form a frosted-glass appearance in the lower third, when superficial vessels appear to produce pannus. Marked folding of Descemet's membrane produces the appearance of a fan at the back of the comea. Corneal sensation becomes diminished. In the anterior chamber microfilariæ swimming in the aqueous, in the focal beam of the slit-lamp, appear as golden wriggling threads; they may even join together and resemble an octopus. In the iris star-shaped patches of connective tissue in the stroma cause local contractures, with atrophy of the iris pigment, producing a spongy appearance, like that of a "pumice-stone iris." A brown mass in the lower part of the anterior chamber is caused by a mass of dead microfilariæ in the aqueous; this leads to a pointed, pear-shaped pupil. Cyclitis is indicated by keratic precipitates and leads to secondary cataract and glaucoma. Cataracts are a frequent source of blindness and are due to deficient nourishment. In the vitreous degeneration of the "asteroid hyalitis" type is present.

Sarkies (1952), in 319 cases of onchocorciasis, found 14 per cent. with microfilariæ in the eye without ocular lesions. Some 16 per cent. showed nummular opacities in which malnutrition may have played a part. Damage to the eyes may be arrested in the early stages by intravenous injections of antrypol. Indications for hetrazan are present after completion of the course. Van Hoof (1947) found that antrypol had a filaricidal action on the adults and microfilariæ. Certainly allergic reactions are less severe in those cases injected with antrypol. In 32 cases with antrypol injections intravenously 1 grm. for 8–9 weeks the effects were remarkably

constant and microfilariæ disappeared from the aqueous between the fourth and sixth weeks.

Retina and choroid.—Here there is a combination of choroidal sclerosis with retinitis pigmentosa. There are large approximated areas of tapetoretinal degeneration, situated posterior to the equator and extending to the disc margin. The retina is abnormally transparent and the pigment is heaped together. In the background streaks, due to the sclera showing through spaces occupied by blocked choroidal vessels, give the appearance of cracked sun-baked mud. In the otherwise normal areas of the retina a few "bone-corpuscle" aggregations of retinal pigment are present. Optic atrophy is seen in all cases with gross choroidal and retinal lesions. There is little evidence that this atrophy has been preceded by more than slight swelling of the papilla.

The greater the distance between the eyes and the localization of the adult parent filariæ, the longer is development of eye lesions delayed.

Diagnosis.—The diagnosis is made by snipping off a piece of skin with forceps near a nodule, placing it in saline solution for 15 minutes at 37° C., centrifuging and then pipetting off the bottom layer with the microfilariæ which have escaped from the tissues. The embryos are thermotactic, and are attracted by heat to the surface of the skin; thus, demonstration is best effected by placing hot fomentations on the skin, and then taking off shavings by means of a Thiersch razor. When these are placed in warm physiological saline, embryos can be detected. Howard recommends placing a powerful electric light bulb a few inches from the skin. No local anæsthetic must be used, and freezing is especially contraindicated. In the eye Ridley recommends the examination of snips of the conjunctiva under cocaine anæsthesia. A portion of the bulbar conjunctiva is seized with toothed forceps and abscissed with scissors.

Intradermal tests.—These tests were carried out by Fülleborn, Rodhain and Dubois with dirofilaria antigen (see p. 750). The results have not been as satisfactory as in other filarial infections. The antigen should be diluted 1:2000 (White and Murdock).

Complement-fixation reaction in onchocerciasis.—Van Hoof employed a complement-deviation test for onchocerciasis, based upon the same principles as other similar tests in filariasis, and he considered that it had done much to remove uncertainties regarding the pathogenic action of this parasite.

The tightly-packed mass of adult parasites is retained when dissected out of the cyst. The filariæ are then cut into thin slices and placed in a desiccator over sulphuric acid, and when dry they are extracted with ether at 25° C.— a process which occupies several days—and are subsequently dried and extracted with alcohol for ten days. The best extracts have an antigenic titre of 1 in 25. It is claimed that the test when put up by the Calmette-Massol technique is so specific that neither Loa loa, A. perstans, nor intestinal helminths are able to vitiate it. The antibodies thus demonstrated are present in serum, cerebrospinal fluid, synovial fluid and cedematous exudates.

The observations so far made on the positive reactions by this test are in favour of the view that certain forms of elephantiasis in the Congo are manifestations of onchocerciasis.

Eosinophilia is not usually marked in onchocerciasis and is therefore not useful as a diagnostic sign.

Treatment.—In the African form the tumours appear to be painless, and may be removed by excision. In the South American form, removal of the tumours under cocaine anæsthesia is said to be followed by an improvement in the ocular conditions within a week or so. Adams (1938) stated that in a European from the Katanga province of the Congo intravenous injections of neostibosan arrested progress of the corneal opacities, but, in comparable cases observed by the Editor, no improvement was noted, so that antimony therapy had to be discontinued. Harris, who gave sodium antimony tartrate intravenously, noted that the microfilariæ disappeared from the skin, in some cases rapidly, when the treatment was continued over a period of four weeks. A useful application to alleviate pruritus is heliobrom (dibromotannate of urea) 10 per cent. in spirit, applied to the skin at night.

Hetrazan.—This drug has been tested out in Mexico and in Guatemala. So far the results have been on the whole favourable. Stoll says that it has a specific and rapid action. The side reactions are common, frequently serious, allergic in character, but of short duration. Herxheimer-like reactions have been recorded with large doses, and are probably due to massive destruction of microfilariæ. Mazzotti and Hewitt state that the most convenient dose is 2 mgm. per kg. three times daily for 21 days; but where the infection is heavy they commence with and of the daily dose for the first day, 2 for the second day and the full dose for the third. It should be given after meals. Should allergic manifestations become severe it is advisable to suspend treatment for 4 days, whilst an anti-histamin drug (Antistin) is exhibited. Hawking (1952) treated 50 onchocerciasis patients in Uganda with hetrazan. The dose was 50 mgm. of dihydrogen citrate-salt 2-8 times daily. The dose was increased after the first two days till 250 mgm., thrice daily, was reached. Violent allergic reactions were produced, though microfilarize usually disappeared from the skin, reappearing directly treatment ceased. Adult worms did not appear to be much affected. When a small dose of hetrazan is given intense reaction in the corium of the skin can be demonstrated. Microfilariæ show evidences of degeneration. These allergic reactions are so constant that they can be used as an additional means of diagnosis.

Combined Treatment.—Burch has shown that the combination of antrypol (suramin) and hetrazan gives the best results in a series of 82 patients.

Antrypol is given intravenously in a course of 8 injections at the rate of 1 grm. weekly. Hetrazan was simultaneously administered in doses of 0.25–2 mgm. per kg. three times daily for 3–6 weeks. Disappearance of microfilariæ from the skin was astonishingly rapid after either drug. After a year's interval only 15 per cent. of the hetrazan series were free from microfilariæ, whereas 87 per cent. of the antrypol series were free. There is therefore some evidence that intravenous injections of antrypol kills off the adult worms.

Antrypol for intravenous use is used as a 10 per cent. solution, starting with 0.5 grm. and gradually increasing to 1 grm. weekly.

Later with Ashburn (1951) he was able to show conclusively that a combination of these two drugs produces a rapid and permanent action upon O. volvulus microfilariæ.

Prophylaxis.—The extirpation of Simulium neavei by means of DDT sprays has been effected by Garnham in the Kakamega district in Kenya (see p. 864) and this method has now been shown to be a practical proposition.

IV. DRACONTIASIS

Synonym.—Guinea-worm.

Geographical distribution.—This important parasite, Dracunculus medinensis, is found in certain parts of Africa and India, and appears to have been imported from America. In Africa it occurs in the Valley of the Nile, Lake Chad, Bornu, and West Africa; it has been observed in Uganda, but not in the Congo basin. It is also found in Persia. Turkestan, Arabia, and in a very limited part of Brazil (Feira de Santa Anna). Formerly it was supposed to be endemic in Curação, Demerara, and Surinam. Dracunculus is not equally diffused throughout this extensive area; it tends to special prevalence in limited districts, in some of which it is excessively common. In parts of the Deccan, for example, at certain seasons of the year nearly half the population is affected; and in places on the West Coast of Africa (Gold Coast) nearly every negro has one or more specimens about him. In Europe, guineaworm is seen only in natives of, or in recent visitors from, the endemic areas. In North America, according to Chitwood, it has been found in the silver fox (Vulpes fulva), the racoon (Procyon lotor), and the mink (Putorius vison), but never in man. In Asia and Africa the parasite is widespread amongst carnivora. In some parts of the Gold Coast this parasite has now disappeared owing to drying up of wells by drought.

Ætiology. The parasite.—The male worm has only rarely been found (see p. 1004). The female measures about 32·5 cm. to 1 m. 20 cm. in length, by 1·5 mm. in diameter. The embryos are somewhat flattened, with a tapering tail, and measure 0·5–0·75 mm. in length by 0·017 mm. in breadth.

Life-history.—The embryos of D. medinensis are shed into water and, swimming about actively, enter the body-cavity of a fresh-water crustacean, Cyclops quadricornis, or allied species, in which they develop until a length of 1 mm.

is attained. (For details, see Appendix, p. 1005.)

Mode of infection.—The metamorphosis of D. medinensis in cyclops was discovered by Fedchenko in Turkestan and subsequently confirmed by Manson in England; but, owing to the colder climate of this country, the metamorphosis takes longer to complete—eight or nine weeks, instead of five weeks as in Turkestan. Fedchenko supposed that cyclops, containing the larvæ of the guinea-worm, was swallowed by man in drinking-water, digested, and the parasite, being then set free, worked its way into the tissues of its new and definitive host.

Later, Leiper showed that when an infected cyclops is transferred to a 2.0 per cent. solution of hydrochloric acid it is immediately killed, but the larvæ, so far from being destroyed, are aroused to great activity, and eventually escape into the fluid, in which they swim freely. From this he conjectured that under natural conditions man becomes infected through the ingestion of cyclops containing these worms, the gastric juice acting on cyclops and larva in the

same way as the hydrochloric acid in his experiment. In order to prove this, he fed a monkey on bananas concealing cyclops which had been infected for five weeks, and which contained fully-developed larvæ. Six months later, when the monkey died, five worms were found in its connective tissues, all possessing the anatomical characteristics of *D. medinensis*.

The evidence is now fairly complete that the life-span of the female dracunculus, before she appears on the surface of the body, extends to about one year. It is not to be supposed that every species of cyclops is an effective intermediary; if this were the case, guinea-worm infection

would have a much wider geographical range.

Pathology and symptoms.—The parasite, on attaining maturity, makes for the legs and feet; these are the parts of the human body most likely, in tropical countries, to come in contact with puddles of water, the medium in which cyclops—the intermediary host—lives. The water-carriers in India are very subject to guinea-worm, which, in their case, appears on the back—that is, the part of the body against which the water-skin lies when being carried. It seems that the mature guinea-worm, by instinct, seeks out that part of the body most in contact with water.

Occasionally, the guinea-worm fails to pierce the integument of her host; sometimes she dies before arriving at maturity. In either case she may give rise to abscess; or she may become cretified, and in this condition may be felt, years afterwards, as a hard convoluted cord under the

skin, or be discovered on dissection.

The haunt of the female guinea-worm is the connective tissue of the limbs and trunk. When mature, she proceeds to bore her way through this tissue, travelling downwards. In 85 per cent. of cases she presents in some part of the lower extremities; occasionally in the scrotum or on the dorsum (Fig. 182) or sole of the foot; rarely in the arms; exceptionally in other parts of the body, or even in the head. In a proportion of cases the appearance of the worm at the surface of the body is preceded by slight fever and urticaria; the onset of the skin eruption is generally at night, before the blister or other localizing signs are noted. Arrived at her destination, the female worm pierces the derma. consequence of some irritating secretion, a small blister, containing, as a rule, numerous embryos, forms and elevates the epidermis over the site of the hole in the derma. The irritation due to this act causes a burning sensation and induces the patient to immerse his foot in water. by the blister ruptures, disclosing a small superficial erosion $\frac{1}{2}$ in. in At the centre of the erosion, which sometimes quickly heals spontaneously, a minute hole, large enough to admit an ordinary probe, is visible. Occasionally, when the blister ruptures, the head of the worm is seen protruding from this hole; as a rule, however, at first the worm does not show. If the neighbourhood of the ulcer is douched with a stream of cold water from a sponge, in a few seconds a droplet of fluid —at first clear, later milky—wells up through the hole and flows over the surface. Sometimes, instead of this fluid, a small, beautifully pellucid tube, the uterus, about 1 mm. in diameter, is projected through the hole in response to the stimulus of the cold water. Apparently in this act the

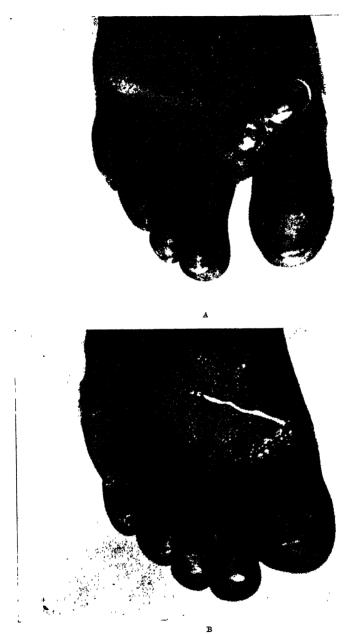


Fig. 182.—Guinea-worm disease. A. primary blister produced by head of female prior to emergence.

B. Female guinea-worm protruding from interdigital cleft, showing terminal expansion containing myriads of embryos.

tissues of the head are exploded in order that the uterus may escape (Fig. 183).

When the tube has been extruded an inch or thereabouts, it suddenly fills with an opaque whitish material, ruptures, and collapses, the fluid spreading over the surface of the erosion. If a little of the fluid, either that which has welled up through the hole, or that which has escaped from the ruptured tube

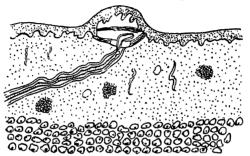


Fig. 183.—Diagram of vesicle caused by guinea-worm, showing prolapse of the uterus in the act of discharging embryos into the blister cavity.

(After Fairley and Glen Liston.)

be placed under the microscope, it is seen to contain myriads of dracunculus embryos lying coiled up, almost motionless, with their tails projecting in a very characteristic manner (Fig. 184). If now a drop of water be instilled

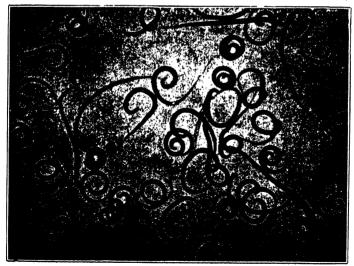


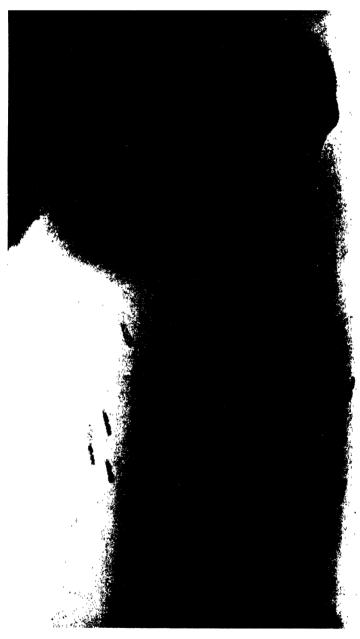
Fig. 184.—Embryos of D. medinensis. (Microphotograph by Mr. H. B. Bristow.) below the cover-glass, the embryos unroll themselves, and, in a very short time, swim about, more suo, with great activity. If the douching be repeated



Radiograph of leg showing guinea-worm injected with lipiodol. (Dr. Botreau-Roussel.)

GUINEA-WORM

PLATE XX



RADIOGRAPH OF CALCIFIED CYSTICERCI IN THE THIGH

(Major-General W. P. MacArthur, Trans. Roy. Soc. Trop. Med. and Hyg., 1934.)
PLATE XXI

after an hour or longer, a further supply of embryos can be obtained; and this can be continued from time to time until the worm has emptied herself. Apparently the cold applied to the skin of the host stimulates the worm to contract, and thereby force out her uterus, inch by inch, until it is completely extruded. The repeated birth of a limited number of progeny each time the skin of the host comes into contact with water is therefore a wonderful provision of nature. Aberrant forms of embryos were described by Moorthy and Sweet (p. 1005).

The first symptoms appear usually simultaneously with the beginning of the blister-formation, and consist of urticaria, nausea, vomiting, diarrhœa, asthma, giddiness and fainting and they are believed to be due to absorption of the toxin mitted by the worm to form the initial skin blister. The symptoms strongly suggest an anaphylactic reaction, and goats injected with guineaworm extracts show similar symptoms, while injections of adrenalin bring about rapid improvement. Later symptoms result from the invasion of the ulcer by bacteria.

Should the worm become injured or lacerated while lying in the subcutaneous tissues, severe local reaction may develop. The part becomes extremely painful, inflamed and cedematous, and cellulitis may result, due to secondary downward growth of staphylococci and streptococci from the skin. Arthritis, synovitis, epididymitis, contractions of tendons, and ankylosis of joints have even been known to ensue. In some patients, generalized systemic symptoms accompany the premonitory urticaria, such as pyrexia, giddiness, dyspncea and vomiting; and gastro-intestinal symptoms have been noted during the early stages of guinea-worm infection, associated with an increase of eosinophile cells in the blood; this is due to the absorption of a specific toxin, so that alarming symptoms may be produced in laboratory animals by intravenous injection of extracts of the adult dracunculus.

That the cellulitis associated with guinea-worm is due to the excretion of toxins by the mature parasite was shown by Fairley and Glen Liston, who failed to produce any local or general reaction by subcutaneous injection of the embryos themselves. Botreau-Roussel and Huard described a specific non-bacterial arthritis, especially of the knee-joint, associated with the presence of a guinea-worm in the vicinity.

Lester from Dar-es-Salaam reported the discovery of an entire guinea-worm coiled in a hernial sac; it was kept alive in the laboratory for twelve days after removal. According to Trewn, guinea-worms may present themselves after as long an interval as fifteen years from the time of infection. Massive infections are also reported, and as many as 56 adult worms have been counted in one person at the same time.

Diagnosis.—This is, as a rule, sufficiently obvious. In cryptic infections there is generally an eosinophilia. If the worms cannot be seen they may be felt underneath the skin. When both these methods fail, screening with X-rays has been of use; and injection of 2 ml. of 10 per cent. collargol into the worm renders it opaque (Hudellet, 1919). Effete and calcified worms are easily demonstrated by skiagraphy. (Plate XXI.)

An intradermal test for diagnostic purposes was introduced by Ramsay. The antigen is obtained by adding to 100 ml. of ether 0·25 grm. of dried powdered guinea-worm, with frequent shakings at room temperature for two hours to remove the lipoids. The dried, ether-free residue is extracted with shaking for four hours, in 100 ml. of 0·85 per cent. solution of sodium chloride at 37° C. After centrifugation, it is passed through No. 6 Seitz filter, and 0·25 ml. of this is used for injection. A positive wheal is 2-3 cm. in diameter, with outrunners.

Sequelæ.—Subacute sterile abscesses are occasionally seen, due to premature death of the female D. medinensis, with the liberation of embryos into the subcutaneous tissue. The condition is diagnosed by the deeply situated fluctuating swelling, not communicating with the exterior. In synovitis and arthritis, the exudate may be serous or purulent. Generally, there is an associated cellulitis, the synovial membrane being involved by direct spread through the adjacent tissues. Permanent deformities and a history of prolonged illness in the recumbent position are invariably associated with sepsis. Bony ankylosis is rare. The joints mainly involved are the knee and the ankle, while the tendo Achillis and hamstrings are not infrequently contracted. Connor (1922) drew attention to cases diagnosed as chronic rheumatism, traumatic synovitis, periostitis or sciatica, where X-ray examination revealed calcified worms.

Treatment.—Formerly it was the custom, as soon as a guinea-worm showed herself, to attach the protruding part to a piece of wood and endeavour to wind her out by making a turn or two daily. Sometimes these attempts succeeded; just as often the worm snapped under the strain. The consequences of this accident were often disastrous. Myriads of young escaped from the ruptured ends into the tissues, and violent inflammation and fever, followed by abscess and sloughing, ensued; weeks, or months perhaps, elapsed before the unhappy victims of this rough surgery were able to get about. Too often, serious contractions and ankylosis from loss of tissue and inflammation, and even death from sepsis resulted.

If a guinea-worm be protected from injury, and the part she occupies frequently douched with water, her uterus will be gradually and naturally forced out inch by inch and emptied of embryos. Until this process is completed she resists extraction. When, in from fifteen to twenty days, parturition is completed, which can easily be ascertained by the douching experiment, the worm is absorbed or tends to emerge spontaneously. A little traction then may aid extrusion. Traction, however, must not be employed so long as embryos are being emitted. When located by X-rays and collargol, the worm may be dissected out (Hudellet).

The parasite may also be killed by injecting her, by means of a syringe, with solution of bichloride of mercury, 1 in 1000; after twenty-four hours, extraction is usually easily effected. If the worm has not shown herself externally, but can be felt coiled up under the skin, the coils should be injected, through several punctures, with a few drops of the same solution. Fairley and Glen Liston advocated aspiration of the blister-fluid before extraction, followed by precautions to avoid sepsis. The surface should first be painted with tincture of iodine. After a period of forty-eight hours, they advised excision of the worm if lying convoluted in a limited space; failing this, intermittent traction should be combined with massage. The subcutaneous injection of 9-10 min. of 1 in 1000 adrenalin hydrochloride immediately relieves the distressing prodromal symptoms, such as urticaria and asthma, from absorption of toxins.

To complete extraction of the worm, the operative procedure is as follows. It is applicable whether a blister has formed or not, or whether a sinus is present. The skin overlying the worm at some distance from the ulcer is infiltrated with cocaine and adrenalin (2 ml. of 1 per cent. cocaine and 1 ml. of 1 in 2000 adrenalin).

An incision is made at right angles to the line of the worm through the anæsthetized tissues. The whitish fibrous sheath of the worm being exposed, the superior surface is incised longitudinally and a small strabismus hook inserted inside its interior. By these means the female D. medinensis is hooked out. The loop of the worm is held tightly in the fingers while intermittent traction and massage are again employed. Should it be impossible to liberate the distal end of the parasite, a second incision is made over another palpable segment of the worm, and both ends of the central loop are cut across and the intermediary portion removed. It is most important that the proximal head portion

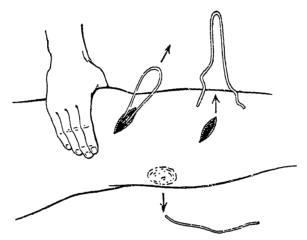


Fig. 185.—Diagram of removal of guinea-worm. (After Fairley.)

of the worm should be removed through the sinus, not drawn through the sheath in the subcutaneous tissues in the reverse direction, or otherwise there will be pollution with organisms from the mouth of the sinus (Fig. 185).

A newer treatment is by a dye, phenothiazine (Mountjoy Elliott, 1942). Finely powdered and triturated, it is emulsified with adeps lance and olive oil. A certain amount of heat is required to keep the solution sufficiently fluid to be drawn up into a hypodermic needle. Each injection consists of 10 ml. of the emulsion, containing 1 grm. of phenothiazine. The site of the injection is anæsthetized by infiltration with novocaine. Three injections are usually made as near the course of the buried worm as possible. Usually, 4 grm. of phenothiazine is given in one treatment, and the site massaged for five minutes. Injections are made at weekly intervals and rarely more than two courses are needed. After 5 to 7 days the worm may be extracted by the rolling stick method. The rolling should be preceded by strong pressure with the fingers along the course of the worm tract in the direction of the sinus. This milking action should be performed for about 2 minutes. No toxic symptoms have been noticed.

Prophylaxis.—It is evident that prevention is merely a question of protecting drinking-water from pollution by guinea-worm patients. Leiper demonstrated that cyclops are killed by raising by a few degrees the temperature of the water in which they live. He suggested heating by a

PARASITES OF THE LYMPHATIC SYSTEM AND CONNECTIVE TISSUES

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portable steam generator the water in wells and water-holes which are known to be sources of guinea-worm infection. Alcock found that the addition of a trace of potash to the water is equally effective. In Mysore, Moorthy found that step-wells are the greatest source of infection, especially in high-caste Hindu houses. When barbel fish (Barbus puckelli, B. ticto, Rasbora donicornicus), which feed voraciously on cyclops, are introduced, the guinea-worm disappears. Otherwise the wells must be treated every fourteen days with perchloron (bleaching-powder substitute).

CHAPTER XLVI

PARASITES OF THE LUNG AND LIVER

I. PARAGONIMIASIS (ENDEMIC HÆMOPTYSIS)

History.—This disease and the characteristic eggs appearing in the sputum of its subjects were described by Baelz and Manson in 1880. Ringer, in 1881, was the first to find the mature parasite, which was afterwards described by Cobbold under the name of Distomum ringeri; subsequently it was recognized to be closely related to the previously described Paragonimus westermanni of the tiger. The main features of its life-history and pathological bearings have been worked out since by Japanese observers. Closely allied species are found in the pig, dog, cat, otter, mink and ichneumon (see Appendix, p. 942).

Geographical distribution.—Paragonimiasis occurs in China, Japan, Korea, Formosa, the Philippines, Nigeria and the Cameroons. Seven cases were reported amongst members of the U.S. Marine Corps from the South Pacific (Samoa and Solomon Islands) during the recent war (Miller and Wilbur). In some of the endemic districts a notable percentage of the population is affected. Paragonimiasis is found in wild animals (racoons and opossum) in the United States, but so far no human infections have been discovered there. The spread of the disease takes place by eggs in the sputum, more usually in the fæces; this is specially the case in cats and other domestic animals.

Ætiology.—The fluke, Paragonimus ringeri (westermanni), is reddish-brown, thick and fleshy, oval, and measures 8-20 mm. by 5-9 mm. Development of the parasite proceeds in the fresh-water snail Melania, and thereafter the larva, or metacercaria, encysts in several species of fresh-water crabs (Potamon and Parathelphusa) and crayfish.

Man is infected by eating raw or improperly-cooked crabs, of which the Koreans are very fond, while the raw juice of crayfish is taken as a medicine for diarrheea and whooping cough. The young parasites hatch in the ileum and in 24-42 hours penetrate the intestinal wall near the jejunum, reach the peritoneal cavity, and make their way to the diaphragm by penetrating the tendinous portion. Travelling beneath the pleura, the larvæ reach and pierce the parenchyma of the lungs, where cysts are found. In other organs they do not reach perfect growth (see Appendix, p. 943).

Pathology.—The lungs do not at first present any unusual appearances but, on looking closely, small brown spots are thickly distributed over the entire surface of the pleura and many tumour-like swellings of a deep red colour, in which the parasites are situated, can be seen. On making a section of the lungs, a larger or smaller number of what are known as "burrows" are discovered scattered about, particularly towards the periphery. These burrows consist of areas, somewhat larger than a filbert, of infiltrated lung tissue in which can be seen a number of tunnels filled with the same material that constitutes the characteristic brown sputum, which may also contain one or two trematodes. The septabetween the tunnels may break down and a considerable cavity thus be produced; and as this occurs in connection with one of the bronchi, with which the tunnels always communicate, it may give the appearance of

a dilated bronchus. One burrow may communicate with another. It is estimated that the number of eggs coughed up in twenty-four hours is over 13,000. Tubercle bacilli and paragonimus eggs are frequently found together.

When first discovered, it was supposed that *P. ringeri* was confined to the lungs, but it may affect the liver, peritoneum, testes, intestine, skin, muscle, and brain. It may cause intramuscular abscesses. In the brain it may form a tunnelled tumour similar to those in the lungs.

Musgrave, in his study of the pathology, pointed out that the peculiar bluish, cyst-like burrows of the parasite occur in many organs and tissues. Infiltration by the eggs produces, especially in serous membranes, little brownish-red patches sometimes visible to the naked eye. The intestinal mucosa is a common seat of infiltration, which gives rise to inflammatory reaction, ending in ulceration and the appearance of eggs in the fæces. The eggs may find their way into the spinal cord, as reported by Robertson, and produce transverse myelitis. At least 100 mature parasites have been found in a psoas abscess. The eggs have been found in large numbers in the urine in a case of pulmonary infection (Weinstein, 1953).

Symptoms.—The symptoms generally begin so insidiously that it is impossible to fix their onset with accuracy. The subjects of endemic

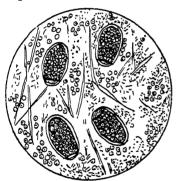


Fig. 186.—Eggs of Paragonimus Westermanni in sputum.

hæmoptysis have a chronic cough and a vague feeling of distress in the chest, which is usually most urgent in the morning on rising. The fits of coughing expel a peculiar rustybrown, pneumonic-like sputum, which can be produced at will almost at any time, and often in considerable quantity. In addition, the patient is liable to irregular attacks of hæmoptysis. Though usually induced by violent exertion, such occasionally come on without apparent cause. The hæmoptysis may be trifling; on the other hand, it may be so profuse as to threaten life or at least to cause intense anæmia.

Ogi stated that an outstanding physical sign in chronic cases is clubbed fingers. The physical examination of the chest is mainly negative. The patient is well-nourished. Resonance is usually normal, with a tendency to hyper-resonance, while râles can be demonstrated in a few instances.

The sputum.—Under the microscope the peculiar colour of the viscid, pneumonic-like sputum is found to be due partly to red blood-corpuscles, partly to a crowd of dark-brown, thick-shelled, operculated eggs (Fig. 186). Besides pus-corpuscles there are large numbers of eosinophil cells. Charcot-Leyden crystals are often present. The eggs vary a good deal in size and shape; they are all distinctly oval, have a yellow, smooth, double-outlined shell, and measure from 80 to 100μ by $40 \text{ to } 60 \mu$. If

the sputum be shaken up in water, and the water be renewed from time to time, in the course of a month or six weeks—longer or shorter according to temperature—a ciliated miracidium is developed in each egg. When the mature egg is placed on a slide with slight pressure on the cover-glass, the operculum is forced back, and the miracidium immediately emerges and begins to swim about and gyrate in the water.

Abdominal symptoms in some cases may also be present; they consist of dull abdominal pains and occasional diarrhea. The abdominal wall feels hard and is tender; at the same time symptoms of liver cirrhosis, appendicitis, enlargement of the prostate, epididymitis and adenitis may

be present.

Cerebral symptoms.—When the disease affects the brain, especially in children, a peculiar form of Jacksonian epilepsy may be a feature for a considerable period, and may end in hemiplegia, aphasia, visual disturbances, homonymous hemianopia, pareses or monoplegias of various degrees.

Generalized.—In what is known as generalized paragonimiasis, in addition to the symptoms noted above, there is generalized lymphadenitis, especially affecting the axillary and inguinal groups, often associated with

cutaneous ulcerations.

Diagnosis.—Diagnosis is at once established by the discovery of the characteristic eggs in the almost equally characteristic sputum. The sputum is sticky, not foamy, and resembles that of pneumonia. Charcot-Leyden crystals are usually present. Râles and other physical signs of lung consolidation are not usually discoverable. If the intestine or liver is implicated, eggs may appear in the stools.

One-sided convulsions or hemiplegic affections in a native of, or a visitor from the countries in which this trematode is endemic, should suggest examination of the sputum on the chance of discovering the parasite. Should eggs be found, there is a strong presumption that the

cerebral trouble arises from a trematode tumour in the brain.

In the endemic zones of paragonimiasis, even in the absence of eggs in the sputum, Musgrave recommended that this parasite should be suspected in cases of chronic epididymitis, enlargement of the lymph-glands or prostate, liver cirrhosis, and skin ulceration. As some of these conditions are also found in *Schistosoma japonicum* infection, the operculated eggs of paragonimus should be carefully distinguished from those of this parasite. The sputum should be examined bacteriologically to exclude the tubercle bacillus. Blood examination usually discloses a moderate leucocytosis of about 15,000 and there is usually no rise in the eosinophil cells.

The cutaneous ulcerations have to be distinguished from those of

oriental sore.

Bercovitz reported that X-ray examinations of the lungs are very disappointing, while lipiodol infiltration shows no cavities, probably because the paragonimus burrows are situated at the periphery of the lung. Wang and Hsieh, on the other hand, described well-defined opacities and isolated infiltrations in various parts of the lung field. American radiologists have described appearances at the base of the right lung simulating early bronchiectasis. By the method of tomography Kershaw and Ross have described more precise appearances. In the antero-posterior and lateral

aspects they find opacities made up of about six contiguous cavities. The fibrous walls are clearly outlined and there is little surrounding pneumonitis.

Ando described a Bordet-Gengou complement-fixation test, using an extract of the body of the adult worm as antigen. This probably, when fully worked out, will constitute an efficient aid to diagnosis in obscure cases. From the clinical aspect paragonimiasis has to be distinguished from bronchiectasis more than any other condition.

Treatment.-So far no means of expelling the parasite from the lungs has been discovered. In cerebral paragonimiasis it might be possible by operation to remove the parasite and associated tumour. and thus afford a chance of recovery in a condition which has hitherto proved fatal. Kobayashi and Ando reported encouraging results with emetine, which is said to lessen the sexual activity of the trematodes. The drug is injected intramuscularly in doses of 1.25 ml. of a 2 per cent. solution four times daily for five days, but it must be used with great caution, especially where there is any myocardial trouble. This was confirmed by Bercovitz, who gave emetine in 1 gr. daily doses for periods of seven days. To and Ko injected carpain subcutaneously, 5 per cent. in normal saline. The total quantities were 0.3 grm. over six days, and 1.1 grm. over 23 days. Bercovitz reported that marked improvement follows lipiodol injections into the bronchi. Yokogawa and Ro claimed encouraging results in experimentally infected dogs with intramuscular sulphanilamide (prontosil). Subsequently they treated nine cases of human paragonimiasis with intramuscular prontosil, 2.5 per cent. solution, giving a total of 60-165 ml., simultaneously with intravenous emetine, 4 per cent., 12-23.5 ml., over a period of seven to seventeen days. Degenerative changes were observed in eggs in the sputum after three days' treatment. Favourable signs were a decrease in the amount of sputum and disappearance of blood. It is claimed that this treatment proved successful in 50 per cent. of cases.

Prophylaxis in this, as in so many other animal-parasite diseases, lies principally in securing a pure water supply for drinking and bathing purposes, and avoiding all uncooked articles of diet, especially crabs and crayfish, which might be supposed to contain the young parasites. The sputum and fæces should be destroyed. In Chosen, Korea, an enlightened Government has waged a campaign against crabs, and has rendered their sale unlawful, while the populace is being educated about the dangers by means of posters and advertisements.

II. CLONORCHIASIS

Geographical distribution.—The trematode responsible for this disease has been found in many Eastern countries, including India, Mauritius, Japan, Korea, Formosa, China, and Tonquin. In South China, Faust and Khaw determined that the fish-raising industry is responsible for the high incidence in Kwantung Province. In Central Japan, according to Katsurada, there are certain districts in which it affects from 56 to 67 per cent. of the population, and Léger found the eggs \$50 per cent. of the natives of the East Coast of Indo-China. A potentially

endemic area has been discovered on the Pacific Coast of California, the infection having been imported by Chinese immigrants, but the disease has not spread, in the absence of suitable intermediary hosts.

Ætiology.—The parasite, Clonorchis sinensis, measures 10 to 20 mm. by 2 to 5 mm.; it is oblong, narrow, flat, and somewhat pointed anteriorly, reddish, and nearly transparent. Development outside the human body takes place in two different intermediary hosts—primarily, a mollusc, Bithynia, usually B. striatula; and secondarily, several species of freshwater fish of the carp family. (For further details, see Appendix, p. 937.)

Pathology.—C. sinensis inhabits the bile-ducts. It thickens the walls of the biliary canals and expands them in places into cavities and diverticula as large as filberts, the walls of which are thickened with fibrous tissue. In these

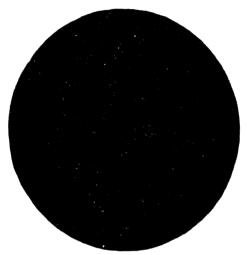


Fig. 187.—Eggs of Clonorchis sinensis in fæces. × 250. (Microphotograph by Dr. John Bell.)

cavities vast numbers of parasites may be found. The diverticula communicate with the bile-ducts, along which the eggs of the parasites, and sometimes the parasites themselves, escape into the intestine. The affected liver is enlarged as a whole, although the tissue in the immediate neighbourhood of the diseased bile-ducts is atrophied. The spleen, also, may be hypertrophied and the intestine in a condition of chronic catarrh. This trematode is sometimes found in the pancreatic ducts, in the duodenum, and in the stomach, associated with ascites, and even with anasarca. According to Hoeppli it may produce carcinomatous changes, while Kown and his associates found new growths in the liver connected with this infection.

This parasite, which for long was supposed to be practically innocuous, is now held to be the cause of a serious cirrhosis of the liver, which may terminate fatally; indeed, there can be no doubt of this in view of the fact that several thousand parasites were present in some cases. Sambuc and Baujean counted 21,000 at one autopsy, and reckoned the total weight of the parasites at 300 grm.

Symptoms.—When the infection is severe the liver becomes enlarged, and chronic diarrhœa, with recurring attacks of jaundice, sets in. Late

anasarca appears, and gradually a cachexia, resembling that of sheep-rot, is established, which, in the course of several years, may prove fatal. In lighter infections there is indigestion, epigastric distress and, sometimes, night-blindness (Bercovitz). The Editor investigated one case in which clonorchis infection appeared to be the inciting cause of acute cholecystitis (strawberry gall-bladder).

An outbreak of clonorchiasis in displaced Europeans in Shanghai was described by Koenigstein, the origin being ascribed to pickled freshwater fish. The clinical picture was one of acute infection, with fever, enlargement of liver and eosinophilia. Eggs appeared in the fæces within four weeks, when the clinical symptoms slowly subsided.

Diagnosis.—It would be well to bear in mind this and other parasites in approaching the diagnosis of obscure hepatic disease associated with diarrhea and jaundice in patients from the East. The discovery of the eggs (Fig. 187) in the stools should give correct diagnosis. Associated with this disease there is generally a leucocytosis of over 30,000 and eosinophilia of over 40 per cent. Toullec and Riou employed the duodenal sound, finding large numbers of eggs in the aspirated bile, even when they failed to demonstrate them in the stools.

Treatment.—The patient should be removed to a non-infected area and given nourishing food. Intravenous emetine has been found of little avail. Several observers (Haeck, Kinugasa and others) injected found intravenously with some degree of success. In vitro experiments have shown that gentian violet, malachite green and Nile blue are lethal to clonorchis in a concentration of 1 in 40,000. The former dye appears to be most effective.

Faust found that, in experimental cats, gentian-violet per os causes death of the fluke after preliminary stimulation of ovulation. About 80 mg. per kilo weight was found to be the correct dosage. Unfortunately in this strength this drug appears to be toxic, though it opens up an

important line of clinical research.

Continuous non-surgical bile drainage has been extensively practised in Korea by means of the duodenal tube. It is found necessary to cocainize the throat to prevent reflex vomiting. As a rule, it is possible to allow the tube to remain in position continuously for several days. During the day-time bile is collected every two hours, following stimulation by 50 per cent. magnesium sulphate through the tube. The bile is examined microscopically for clonorchis eggs, and the number per 4 cu.mm. counted. It is however, necessary to state that this procedure does not remove all the eggs, but it is useful in getting rid of toxic material, and the results are most spectacular when the liver is enlarged and tense. Biliary drainage is not always harmless, and is sometimes followed by shock.

Prophylaxis.—Manifestly, the Chinese habit of eating raw fish should be deprecated. The addition of vinegar does not kill off the clonorchis cysts. Animals and men harbouring the parasite should be prevented from fouling water, whether used for drinking, bathing, or agricultural purposes. The freshwater snails which serve as intermediary hosts inhabit the ponds in which edible fish are cultivated by the Chinese.

CHAPTER XLVII

INTESTINAL PARASITES

I. ASCARIASIS

Definition.—This is infestation of the alimentary tract with the roundworm, *Ascaris lumbricoides*. This worm is large and familiar; it may give rise to no special symptoms save inconvenience, but may be the starting-point of severe complications. The worm and its life-history are described on p. 968.

Symptoms.—The normal situation of ascaris in the bowel is the jejunum. There, as can be shown by skiagraphy, the worms lie motionless, curled up in bundles, so that the bowel can be stuffed with worms like a wellfilled sausage. The worms ingest the barium, and their situation is clearly shown by the opaque outline of the intestinal tract. Toxic symptoms are probably attributable to ascaron, a mixture of albumoses and peptones. Fülleborn and Kikuth studied the allergic phenomena of ascaris infestation. These are well known. Some individuals manifest a peculiar sensibility to ascaris emanations, and entry to the laboratory where ascaris worms are being dissected is enough to cause conjunctivitis, urticaria, asthma, and even "fever." The skin of these people is extraordinarily sensitive to minimal doses of ascaris substance, and in a few minutes a red and extremely sensitive wheal is produced. The passage of a worm is attended by an intolerable itching at the anus and vomiting may cause cedema of the glottis. In children, ascaris infestation may produce pallor of the face, with blue rings under the eyes and sometimes interference with nutrition; on the other hand, the infestation may never be suspected, until eggs are found in the stools.

In many instances the ascaris gives rise to no very noticeable symptoms; in others it is credited with a number of ill-defined gastric and perhaps nervous troubles—capricious appetite, foul breath, restless sleep, peevishness, vague abdominal pains, nausea, and so forth. It may cause most pronounced urticaria. Sometimes the worms get into the stomach and are vomited, giving rise to no inconsiderable alarm. They may even creep up the esophagus into the mouth, or out by the nostrils, and cause suffocation by wandering into the rima glottidis. When aggregated into masses in the intestines they may cause volvulus, or even intestinal Severe lesions of the intestinal wall have been observed where macerated worms have been found in the lumen. They have been known to enter the pancreatic and bile ducts, giving rise to jaundice and abscess of the liver; to cause acute hæmorrhagic pancreatitis by blocking the duct, especially in cases where the papilla of Vater has been damaged by chronic inflammation; to penetrate the intestinal wall and escape into the peritoneum, causing peritonitis (in one Chinese quoted by Hsü, over 1,500 ascaris were removed from the peritoneal cavity); or to burrow into the abdominal walls and cause localized abscess. Eggs have been demonstrated in pearl-like nodules encysted in the peritoneum and mesentery. The worms may invade the lumen of the appendix, which may be packed with eggs, and cause appendicitis. In women, they may invade the generative tract, and have been found encysted in the Fallopian tubes. In children there is characteristically a protuberant abdomen; normal digestion is disturbed; there is loss of appetite and sometimes insomnia. The most common complaint is intermittent intestinal colic. In children in Colombo, Fernando has described several acute types as follows: (a) toxic or cerebral, simulating encephalitis or meningitis; (b) acute abdominal, mimicking appendicitis; (c) respiratory, with sudden onset, dyspnæa and pyrexia.

Although "ascaris pneumonia" is not often diagnosed it has often been suspected in West Indian negroes. In experimental animals heavily infected with ascaris larvæ, death takes place from pneumonia after four to five days. The larvæ, in their wanderings through the lung capillaries, give rise to considerable disturbances and cause intrapulmonary hæmorrhages. In North America pneumonia is much feared by some breeders of pigs, as the ascaris of the pig is very similar to, and has the same life-history as Ascaris lumbricoides. This ascaris is a definite biological species, as it cannot develop to maturity in man.

Koino, a Japanese investigator, swallowed 2,000 ripe human ascaris eggs, Six days later he was attacked by definite pneumonia with dyspnœa, cyanosis. eosinophilia and pyrexia of 104° F. which lasted soven days. The syndrome of tropical eosinophilia seemed to be reproduced (see p. 700). The sputum was profuse from the eleventh to sixteenth days, and contained ascaris larvæ, of which 202 were counted. The liver was enlarged; there was congestion of the conjunctiva, and severe muscular spasms. After a period of fifty days from the time of infection, 667 ascaris, varying in length from 3–8 cm., were voided. It is said that during their migrations in the lung the larval worms may give rise to hæmoptysis.

It is estimated that each female ascaris in the bowel produces 2,000 eggs for every gramme of fæces.

Diagnosis.—It is well, when puzzled over some obscure dyspeptic condition in tropical patients, to bear the ascaris in mind. The stools ought to be examined with the microscope. Various concentration methods may be employed for demonstrating them (see p. 1083). If they are found, a dose or two of santonin may clear up the diagnosis and cure the patient.

Ascaris infestation is usually associated with an eosinophilia, but this is by no means so reliable as was formerly considered, and the Editor has seen heavy infestation without any increase of these cells. During the invasion stage, when the larvæ are resident in the lungs, there is a very definite eosinophilia, but this diminishes as the worms enter the intestinal canal. In America, Jeller, Kaspari and Leathes found in European children an average eosinophilia of 9.9 per cent. and in negro children about 5.3 per cent.

Skiagraphy can be employed in diagnosis. Films taken four to six hours after an opaque meal display ascaris as a cylindrical filling defect, or as a string-like shadow produced by opaque substance which the worm has swallowed. As a rule, the worms are arranged parallel to one another in hundles. (Plate YYII)

in bundles. (Plate XXII.)



ASCARIS LUMBRICOIDES

Radiographic appearances of Ascaris lumbricoides in the small intestine. Barium meal after evacuation. Note worms of various stages. The barium is retained in the intestine of the worm thus giving it a linear appearance. (Dr. T. V. Crichlow).



TREATMENT

The most widely employed drug for the treatment of ascaris is santonin, but it is by no means as effective as was formerly thought, and is apparently more lethal to female than to male worms, while it has been proved that even after several treatments the worms may not be completely eradicated. It is apparently effective to a limited extent when given in suppositories. The dose by the mouth is $\frac{1}{2}$ -1 gr. (0.032 to 0.065 grm.) for a child, and 3-5 gr. (0.194 to 0.324 grm.) for an adult. A good method is to prescribe three doses on successive nights, the first and the last dose followed by castor oil the next morning.

An alternative method consists of taking santonin, gr. 5, with calomel, gr. 2-3, on three successive nights followed by a saline purge, 3ss of magnesium sulphate, two hours afterwards. As children in the tropics are more usually infested with ascaris than are adults, it is necessary to adapt the dosage to their age according to the generally accepted rules; it may be one quarter or one fifth of those stated.

The dose is best prescribed with sugar and 3.5 gr. of calomel for an adult. It is more active in a mixture with castor oil such as:

Santonin .		gr.iv (0.259 grm.)
Ol. ricin		3iii (10.65 ml.)
Mucil. acac		3iv (14.21 ml.)
Syrup. simp.		3i (3.55 ml.)
Aq. menth. pip.		3iss (42.63 ml.)

This is taken after fasting in the morning.

Oil of chenopodium may be given in a mixture with liquid paraffin (one ounce) or in capsules. The maximum adult dose is 24 minims (1·421 ml.), and is usually given in two portions of 12 minims each within a quarter of an hour. Capsules of oil of chenopodium usually contain three minims each of the drug. Eight of these should be given early in the morning, in two portions of four capsules each. Jeliffe (1950) warns that this drug may cause fatal liver damage in African children. Castor oil is contraindicated.

Tetrachlorethylene is given as for ancylostomiasis, with the same precautions (see p. 809). It is given alone, in capsules, in syrup, or with liquid paraffin in doses of one drachm for an adult and proportionately less for children. It should be preceded the night before and followed by a dose of salts such as half an ounce of magnesium sulphate.

Combined treatment, oil of chenopodium together with tetrachlorethylene, is efficacious. They may be given together in a mixture, as in ancylostomiasis, but it is probably best to give the tetrachlorethylene on one day, and the oil of chenopodium on the following. The worms, when expelled, are always dead and sometimes disintegrated. It is important to warn the patient that they may not appear in the dejecta for two, or even three days, after completion of the treatment. Fatalities from carbon tetrachloride treatment, as formerly prescribed, in ascariasis have been reported, probably due to blockage of the bowel or of the bile-ducts by masses of dead worms.

Hexylresorcinol.—In America this drug has come into favour as a vermifuge for ascaris. Crystals in gelatin capsules, or sugar-coated pills, are given by the mouth in doses varying from 0·1-1 grm. three times daily, according to the age

of the patient (0·1 grm. for each year up to ten). The drug should be given on an empty stomach and should be followed by a saline purge. This is the treatment of choice in heavy infestations, where it is advisable to kill off the worms slowly and to avoid toxic absorption.

Pereira (1949) prefers hexylresoreinol in mass treatment in country districts as a single dose is sufficient. (The compound, 2-cthyl-4-chloro-6-hexylresoreinol appears to be more active.)

Hetrazan citrate.—Loughlin and colleagues have established that this drug is the anthelminthic of choice for ascaris; 91–94 per cent. of worms were removed in worm bundles of as many as 226.

Tablets are given in doses of 6 mgm. per kg. three times daily for five days. The best method, however, is a syrup of hetrazan in doses of 13 mgm. per kg. on the first day and 20 mgm. per kg. on the second and third days, or, alternatively, in single doses of 13 mgm. per kg. for four days. Hetrazan has no effect on other intestinal nematodes or cestodes. These results have been confirmed by Oliver-Gonzalez and others.

Prophylaxis.—The prophylaxis of ascariasis is essentially one of efficient sanitation, and the same principles apply as in ancylostomiasis. Vegetables grown by native gardeners who use night soil as manure form an important source of infection. The pit latrine is the most valuable method of right soil disposal, and it has been found that the ascaris eggs are all killed in six months. **Itimeran*, a coal-tar preparation containing organically combined sulphur, has been found effective in killing off ascaris eggs, and is useful for latrines in the tropics. Ascaris prevalence constitutes the most sensitive measure of efficient sanitation. Only, when 100 per cent, of the population use latrines regularly, can any appreciable effect on the amount of ascaris infestation be observed.

TRICHTURIASIS

Trichuris trichiura, the whipworm (see p. 984), is a very common intestinal infestation in the tropics and is a constant cause of cosinophilia. Although generally asymptomatic, Craig and Faust express the view that exeptionally heavy infections may suggest ancylostomiasis. The most important signs are diarrhea, blood-streaked stools, weakness, pallor, emaciation, anamia and abdominal distension. Getz has examined such subjects by sigmoidoscopy and finds the whole wall of the lower descending colon and sigmoid covered with a coat of living worms. Jung and Jeliffe (1952) consider that the clinical picture is closely related to the number of worms present in the bowel. Pain and discomfort referred to the right lower quadrant of the abdomen is constant. Hyperinfection with these worms eventually results in rectal prolapse when the worms may be actually seen attached to the prolapsed bowel. It is estimated that a worm load of 1,000 worms produce 100 eggs per 2 mgm. of fæces.

Treatment of this infestation is not very satisfactory. Kouri and his colleagues in Cuba claim that the best success in expelling the worms is by milk extracted from various species of Ficus (F. glabrata, or F. laurifolia) and this is known as Leche de Higueron. Extracts too from the pawpaw (Carica papaya) are also recommended. Retention encunata of 1:300 hexylresorcinol (one pint), suspended in 10 per cent. solution of barium sulphate, have also been recommended. This should be retained for ½-1 hour. The buttocks and thighs should be given a protective coating of petroleum jelly to prevent burning of the skin by hexylresorcinol. On the day before the patient is given a liquid diet and an evacuating enema at 9.0 p.m.; chloroquine (aralen) by mouth and suspended in retention enemata is said to give good results. (Basnuevo.)

II. ANCYLOSTOMIASIS¹

Synonyms.—Uncinariasis; Hookworm Disease; Egyptian Chlorosis. **Definition.**—A disease in its more pronounced forms characterized by great anæmia, debility, and cardiac incompetence, due to blood destruction by *Ancylostoma duodenale* and *Necator americanus*, nematodes which inhabit the small intestine, and may be present in enormous numbers. The ancylostome amounts to a positive curse in many tropical countries, on account of the dangerous cachexia—ancylostomiasis—to which it gives rise.

History.—The worm, now known as Ancylostoma duodenale, was first recognized by Dubini in 1838, and in 1843 he published a detailed account of it, but apparently did not recognize its pathogenic importance. Bilharz (1853) and Griesinger (1854) connected the parasite with the extremely severe chlorosis prevalent in Egypt, but it was not until the very fatal epidemic of anæmia among the miners in the St. Gothard Tunnel (in 1880) had called the attention of European observers to the subject, that the importance of this parasite as a pathogenic agent legan to be properly apprehended.

Geographical distribution.—The ancylostome has been found so widely diffused that it may be said to occur in all tropical and subtropical countries. It occurs in Belgium, and was found by Haldane to be the cause of an epidemic of severe anæmia in a Cornish mine. In northern countries it is rare; but it is abundantly present in the south of Europe, and in the tropical and subtropical regions of Asia and America. It is especially prevalent in Egypt, Siam, South China, and Malaya. In India, Ceylon, and the East Indies it is a source of grave disability in plantations, mines, etc. It occurs abundantly on most of the Pacific islands, and exists in North and South Queensland.



Fig. 188.—Ancylostoma duodenale.

Nat. size. (Dubini.)

a, Male; b, female.

Ætiology (Fig. 188).—The normal habitat of A. duodenale is the small intestine of man, and particularly the jejunum; less so the duodenum, rarely the ileum or lower reaches of the alimentary canal; very occasionally, it is found in the stomach. In these situations it attaches itself by means of its powerful buccal armature to the mucous membrane, from the blood of which it obtains a plentiful supply of nourishment. It is supposed to shift its hold from time to time, the abandoned bite continuing to ooze blood for a short period. It is said to be very prodigal of the blood it imbibes, the red corpuscles passing through its alimentary canal unchanged, and the plasma alone being utilized.

The male and female ancylostomes—present generally in the proportion of one of the former to three of the latter—do not differ so much in size as do many of the other nematodes. The male (Fig. 188, a) measures 8-11 mm. by 0.4-0.5 mm.; the female (Fig. 188, b) 10-13 mm. by 0.6 mm.

Necator americanus closely resembles A. duodenale, but is shorter and more

¹ A complete bibliography on this disease has been published in a volume by the Rockefeller Foundation International Health Roard. Publication No. 11.

slender (see Appendix, p. 973). At first it was thought to be confined to the American continent, but it has been found by Looss and others in pygmies from Central Africa, and by others again in Rhodesia, India, Ceylon, Fiji, the Philippines, and elsewhere. Near Darjeeling in India it is found as a pure infestation (Lane), whilst in Egypt A. duodenale occurs alone.

The life history of these two parasites is identical.

Reproduction and mode of infection.—The female ancylostomes produce a prodigious and never-ending stream of eggs, which pass out in the fæces. In the body of the host the development of the embryo within the egg does not advance very far; but on leaving the human host it proceeds. in suitable circumstances, so rapidly in the egg that in one or two days a rhabditiform embryo is hatched. This minute organism is very active. voraciously devouring what organic matter it can find and, for a week, grows rapidly and moults twice. After the second moulting it passes into a torpid condition, in which it ceases to eat, and growth is suspended. In this state it may live for weeks or months, moving about more or less languidly in mud, or in damp earth, but it is rapidly killed by drying. It is said that it may also enter drops of dew on blades of grass. and others demonstrated that the larvæ lose their sheaths while living in the soil, and continue to exist unsheathed. Arrived in its final host after moulting again at the end of five weeks, it acquires sexual characters and the permanent adult form.

Infestation is aided by indiscriminate defacation, moist loamy soil, adequate shade and bare feet. There is special danger in badly-used or badly-constructed latrines and infected soils in plantations and gardens.

Looss demonstrated that the larve reach the intestinal canal by boring their way through the skin. From the subcutaneous tissue they enter the blood-vessels and lymphatics, and by this channel are passively transferred to the lungs. Here they leave the capillaries, enter the airvesicles, and thence along the bronchi and trachea pass into the esophagus, and so to the stomach.

The duration of the life of A. duodenale in the intestine has not been determined; some state it in months, others in years (Sonsino)—one to three. The Editor has reported one case in which the life span was proved to be seven years. On account of liability to reinfestation, this point—an important one in prognosis—is difficult to determine.

The exact number of ancylostomes necessary to produce symptoms has exercised much attention. Some consider that 100 are necessary to produce pathogenic effects and that 500 to 1,000 worms must be present for at least six months to produce well-marked hookworm disease. Others believe that very few ancylostomes, ten or so, may affect the general health and working powers.

According to Lane, the egg-laying capacity of a single female ancylostome is about 30 eggs per ml. content of fæces per diem. Sweet, as the result of his studies in Ceylon, concluded that the average Cingalese has an intensity rate of hookworm infestation of 2,200 eggs per grm. "basis-formed fæces," or as representing approximately one hundred ancylostomes. It is estimated that 53 per cent. of people have what is classified as "hookworm disease," the remainder being merely "carriers of worms."

In four persons from whom the worms were recovered the average egg-output per day for each female worm was 28,080. Relatively it appears that the egg-count falls as the worm-count rises.

Pathology.—The exact rôle of the ancylostome worm in the production of anæmia is by no means settled. The following theories have been put forward of the causation of anæmia:

- (a) Chronic loss of blood.
- (b) Absorption of specific toxin.
- (c) External conditions, such as diet and general hygiene.
- (d) The damaged gut may play a rôle through repeatedly renewed bacterial infection.

On the whole, evidence points to the dietetic factor as playing the chief part in the reaction of the human body to this infestation. As already mentioned, the bodies of the victims of ancylostomiasis are not wasted; on the contrary, there is plenty of fat in the usual situations. The appearance of plumpness is further increased by a greater or lesser amount of general ædema. There may be effusions in one or more of the serous cavities. All the organs are anæmic. The heart is dilated and flabby, its muscular tissue being in a state of pronounced fatty degeneration. The liver also is fatty, and so are the kidneys.

If the post-mortem examination be made within an hour or two of death, the ancylostomes, in numbers ranging from a few dozens up to many hundreds, will be found still attached by their mouths to the mucous surfaces of the lower part of the duodenum, of the jejunum, and perhaps of the upper part of the ileum; but if the examination has been delayed for some hours the parasites will have loosed their hold, and are then found lying in the mucus coating the inner surface of the bowel. Many small extravasations of blood-some fresh, others of long standing-are seen in the mucous membrane, a minute wound in the centre of each extravasation representing the point at which a parasite had been attached. Sometimes, blood-filled cavities, as large as filberts, are found in the mucosa, each cavity enclosing one or two worms and, probably, communicating by means of a small hole with the interior of the intestine. Old extravasations are indicated by punctiform pigmentation. Vesiculations and thickening of the mucosa may be evidence of a greater or lesser degree of catarrh. Occasionally, streaks or large clots of blood are found in the lumen of the bowel. The hookworms are thought to inject toxins from their oral glands; they certainly secrete some anti-coagulant substance. The actual sucking of blood is the most important factor, added to the fact that the worms frequently move from spot to spot. The iron-grey colour of the worms is due to the deposition of hæmosiderin granules in their intestine; sometimes they are red from freshly imbibed blood.

In acute cases eosinophilia is high, but gradually diminishes. Achlorhydria is comparatively common. In the chronic form of the disease the Van den Bergh reaction is negative. The average red cell count is 2,900,000 per c.mm., and the hæmoglobin 37 per cent. (Haldane). The average diameter of the red cells is $7.44~\mu$ with reticulocytes less than 1 per cent. The hæmoglobin deficiency is not really as gross as suggested, because there is considerable increase in blood volume and the reduction in total hæmoglobin is much less than that suggested by the percentage figure. The average total blood-volume is 79.5 ml. per kg. body-weight (normal 85 ml.); the average plasma volume in ancylostome anæmia is 62.6 ml. per kg. (normal 50 ml.), so that the diminution of the total blood-volume can be accounted for entirely by the diminution of the red blood-corpuscles. The blood-picture is therefore that of a secondary microcytic anæmia, which is to a great extent curable by iron therapy.

Microscopical examination of the liver and kidneys shows the presence, within the cells of the parenchyma, of grains of yellow pigment having the reactions of hæmosiderin. The bone marrow is hyperplastic: erythropoïesis being dominant.

Symptoms.—There may be dozens of ancylostomes in the intestine without any appreciable amenia, or, indeed, symptoms of any description whatsoever. Grave symptoms are the exception. It is important, therefore, to avoid concluding that the ancylostome is the cause of every patho-

logical condition with which it may chance to concur.

On the other hand, many inhabitants of tropical and subtropical countries are in a state of chronic starvation. Living on coarse, bulky, innutritious food, they are liable to dilatation of the stomach and dyspeptic troubles. Any additional cause of malnutrition, such as a swarm of ancylostomes and a daily though perhaps small loss of blood, may be sufficient to turn the scale against them. In those countries, as elsewhere, there are many who live just on the borderland between health and disease; to such the ancylostome may prove "the last straw that breaks the camel's back." It is evident that, as a complication of typhoid, of kidney disease, of dysentery, of malaria, in fact of any chronic or exhausting disease, the importance of this anæmia-producing parasite cannot be ignored.

The practitioner in the tropics, therefore, must be constantly on the look-out, in all cases of anamia, dyspepsia and debilitated conditions generally, for the ancylostome. He must bear in mind that this parasite, if permitted to remain in the intestine for any length of time, may be the cause not only of remediable anamia, but of irremediable anamia-produced degenerations of various organs. On this account, also, its early recognition becomes a matter of the first importance. It has been pointed out by many observers that ancylostomiasis is the source of considerable surgical risk, not only in rendering the operative procedure more difficult, but also in retarding convalescence. It is also said to increase the risk of delayed chloroform poisoning. Whenever possible, anthelminthic treatment should be instituted before operation, especially laparotomy.

Further, ancylostomiasis is an important disease from the standpoint of the employer of native labour. The invaliding and inefficiency which it causes among coolies, not to mention the deaths, are often a serious financial matter to the planter and the mineowner. To them any wisely directed expense or trouble undertaken for the treatment and control of this helminthiasis will be abundantly repaid by the increased efficiency

of the labourer.

The essential symptoms of ancylostomiasis are those of a progressive anæmia—an anæmia which is generally associated with dyspeptic trouble, but which, in uncomplicated cases, is not associated with wasting. If the progress of a case be unchecked, serous effusions and fatty degeneration of the heart ensue, and death may occur from syncope or from intercurrent complication. CEdema may be localized, or there may be general anasarca, Most commonly it is confined to the face or legs.

Hill and Andrews (1944) consider that those patients with signs of cardiac abnormalities are in fact suffering from nutritional complications, whilst Heilig has pointed out the difficulty of differentiating between

decompensated mitral disease with right heart failure and cardiac lesions induced by ancylostomiasis.

There is a decrease in the total plasma protein and plasma albumin, with increase of globulin. The albumin-globulin ratio is usually less than one. The cedema is due to reduction of colloidal osmotic pressure due to decrease of albumin, which, in turn, is the result of deficient absorption.

Ground itch or ancylostome dermatitis is usually the first symptom noted (see p. 813), but one of the earlier is pain or uneasiness in the epigastrium. This is generally increased by pressure, but for the time may be relieved by food. In some people it may produce an acute and ever-present epigastric pain, which closely resembles duodenal ulcer and may often be mistaken for it. The appetite, sometimes defective, is more often ravenous, though its gratification is apt to give rise to dyspeptic trouble of various kinds—to colic, to borborygmi, and perhaps to diarrhea of imperfectly digested food. Constipation may be present in some instances, irregularity of the bowels in others. The taste may be perverted, some patients exhibiting and persistently gratifying an unnatural craving for such things as earth, mud, or lime—what is called pica or geophagy. The stools sometimes, though rarely, have a reddish-brown tinge from admixture of half-digested blood. Sometimes they may contain small flakes of blood-tinged mucus. Pure blood is seldom passed; and an extensive hæmorrhage, unless there be concurrent colitis, is rare, although, post mortem, quantities may be found in the small intestine. In the quiescent period the occult blood test is positive. Fever of an irregular. intermitting, or even a subcontinued type is common. On the other hand, the temperature may be constantly subnormal, or these conditions may alternate. After a longer or shorter time, symptoms of profound anæmia gradually disclose themselves. The mucous surfaces and the skin become pallid, the face is puffy; and the feet and ankles are swollen: All the subjective symptoms of a definite anæmia now become more and more apparent; there are lassitude, breathlessness, palpitations, tinnitus, vertigo, dimness of vision, mental apathy, depression and liability to syncope. The circulation is irritable, and hæmic bruits can be heard over the heart and larger blood-vessels. Ophthalmoscopic examination may reveal retinal hæmorrhages.

Some of these symptoms, were it not that with the advancing anæmia there is no loss of weight, might suggest the possibility of tuberculous or cancerous disease or Bright's disease. Though hæmocytometric estimates testify to a slow and steady fall in the blood corpuscles until the lowest limit compatible with life is reached, there is no true poikilocytosis as in idiopathic pernicious anæmia, no excessive leucocytosis as in leukæmia, and not necessarily any enlargement of lymphatic glands, liver, or spleen. There is generally a marked eosinophilia of about 7-14 per cent., though in rapidly fatal cases these cells tend to disappear. The depression in the hæmoglobin value of the corpuscles is considerably greater than the fall in their number.

The rate of progress is very different in different cases. In some, a high degree of anæmia, and even death, may result within a few

weeks or months of the appearance of the first symptoms. Such rapid cases are rare; more frequently the disease is exceedingly chronic, ebbing and flowing, or slowly progressing, through a long series of years. Acute cases develop terminal diarrhea with passage of much mucus and, occasionally, blood, and are apt to be mistaken for various forms of dysentery.

Should such serious ancylostomiasis occur before puberty, the growth and development are apt to be delayed

and stunted (Fig. 189).

There appears to be some reason for the belief that after generations of exposure to this infection a certain degree of tolerance is attained.

It is not surprising that the severe nutritional changes associated with ancylostomiasis affect the mental powers of an afflicted population. Prolonged exposure in the European has led to the production of a race known as the "mean white," stunted both in mental and in physical capacity. In Jamaica, in districts where the whole population suffers from ancylostomiasis, not only are the people intensely indolent, but they are also predisposed, on this account it is said, to larceny and other crimes.

The practitioner in the tropics should always be on the look-out for subacute infestations in Europeans on plantations and in mines. This does not apply solely to the men, but to their wives and children as well. Minor degrees of anæmia. an undue tendency to fatigue, lassitude and digestive disturbances are to be ascribed to this infestation, even where, from the habits of the patients, it might not be suspected. In Europeans undoubtedly the infestation may take place via the mouth and alimentary tract, but European children who are apt to play in sand, often used as a site for defecation by natives, become infested in the usual way, via the skin.

Ancylostomiasis and pregnancy.

—Wickramasriya found that hookworm

disease exerts a deleterious influence on pregnancy, and that in heavily infested districts it is the most common cause of repeated abortions and miscarriage. Moreover, a heavy maternal and feetal mortality is associated with it, and early interruptions of pregnancy and neonatal



Fig. 189.—Ancylostomiasis in a South American Indian boy, showing stunted growth, characteristic facies, and protuberant abdomen. (By permission of the Rockefeller Foundation.)

deaths are also included among its effects; it is estimated that the combined feetal and infantile mortality from this cause is almost 60 per cent. In the absence of skilled treatment, the chances of a successful pregnancy are remote, if the hæmoglobin percentage has fallen below 60 at the commencement. Women who are heavily infested show a predisposition to toxæmias, such as pre-eclampsia and nephritic toxæmia.

Impaired renal function is an outstanding feature in the majority of expectant mothers suffering from ancylostomiasis. They must be regarded as persons with a lowered renal reserve who may enter into the stage of "decompensated impairment of renal function" with the onset of gestation. There exists great danger of death from post-partum shock, if the hæmoglobin percentage has fallen to 30 or under at the time of labour. Fisk found numbers of A. duodenale in the intestine of a child a month old who died of this infestation.

Diagnosis.—Provided it is suspected, ancylostomiasis is easily diagnosed. In tropical countries, in patients coming from tropical countries, and in miners who work in very warm mines in cooler climates. anæmia with concurrent eosinophilia should always suggest a microscopical examination of the fæces (see Appendix, p. 1081). The dyspeptic symptoms may simulate those of duodenal ulcer and it has been noted that sometimes free acidity shows a higher rise than that usually observed and that high levels may be maintained in spite of varying degrees of severe anæmia. If the eggs of A. duodenale or of N. americanus are discovered, and no other reason for the anæmia is made out, the presumption is that one or the other of these parasites is responsible; at all events, no harm is likely to result from treatment based on this supposition. On the other hand, if no eggs are found, it must not be concluded that the case is not one of ancylostomiasis: for sometimes, in the later stages of the disease, symptoms will persist although the parasites which caused them in the first instance have disappeared spontaneously, or have been got rid of by treatment. The usual method of diagnosis by microscopic examination of simple smears of stools does not convey a quantitative idea of the severity of the infestation. The grade runs from one to a thousand or more worms. Fæcal diagnosis has been rendered more accurate by the method of Clayton Lane, known as the flotation concentration method (see pp. 1082-1083), and by other techniques. In the majority of cases a test for occult blood in the fæces is positive, and Charcot-Leyden crystals are frequently found.

TREATMENT

General statement.—Several forms of treatment have been introduced for killing and expelling the ancylostome worms. These drugs necessarily contain a toxic principle, and considerable care should be exercised in their administration.

I. Oil of chenopodium (Chenopodium anthelminticum = goosefoot, wormseed, "Jerusalem Oak"). The active principle against ancylostomes or ascarides is ascaridole (45-70 per cent.), $C_{10}H_{16}O_2$, which is unstable, but which in 1 in 10,000 of oil kills the worms. It has a sharp, burning, nauseating taste, and is put up in hard gelatin capsules. The

absorption of this substance is very rapid, and in toxic doses it causes depression of the respiratory centres. Excretion of ascaridole takes place mainly through the lungs. It is to be used with caution in cases with cardiac hepatic, or visual disorders, and is definitely contra-indicated in pregnancy. nephritis, organic heart disease, hepatic dysfunction and intestinal ulceration. The maximum dose which can be given with safety is 3 ml. in three gelatin capsules of 1 ml. each at intervals of one hour. It is well tolerated by healthy individuals in hospital. For routine the dose is 1.5 ml. (24 min.) in capsules containing 3 minims (0.177 ml.) each. Eight of these capsules should be given-in two lots of four capsules at an interval of half an hour. For children, the dose should be 1 min. for each year of age up to 16. The drug should be administered three hours after a light meal. A quarter of an hour after it a strong saline purge (sodii sulph. 1 oz.) is given, with the object not only of washing the unabsorbed portion of the drug out of the intestine, but also of expelling the partially paralysed worms. Some prefer caster oil, but others consider that it tends to increase the absorption and add to the toxicity. A repetition of oil of chenopodium treatment should not be undertaken in less than a week.

Probably oil of chemopodium is more effective against Necator americanus than against A. duodenale.

II. Carbon tetrachloride (CCl₄—tetrachlormethane, tetraform), a drug closely allied to chloroform, was originally introduced by Hall as a vermifuge and has been found suitable for the mass treatment of ancylostomiasis, but has now to a great extent been superseded by tetrachlorethylene.

Carbon tetrachloride is used as a solvent in rubber, chemical, pharmaceutica. and paint industries, as a cleansing agent, as fire-extinguisher, insecticide sprays and soap solutions. It has also been used as a hair shampoo. It is a colourless. volatile, chloroform-like liquid with a pleasant quince-like odour and a specific gravity of 1.6. It is slightly soluble in water, and freely miscible in alcohol, oils. and other substances. When manufactured by direct chlorination of carbon bisulphide, it may contain traces of the latter drug. It exerts a preliminary burning effect on the nucous membrane, followed by anæsthetization. On exposure to light and air, earbon tetrachloride slowly oxidizes with the formation of poisonous substances, phosgene or carbonyl chloride (COCI₂), and it should therefore be kept in dark and tightly stoppered bottles. Absorption occurs from the stomach and intestines, but after large doses most of the drug is passed out in the fæces, combined with fats and fatty acids. Absorption in the body is by the lymphatic and portal routes, producing dizziness and drowsiness. Absorption may be followed by signs of liver damage; jaundice may be seen on the second day after administration. Calcium chloride in full doses has a marked effect in controlling toxic symptoms. Acute carbon tetrachloride poisoning produces a board-like rigidity of the abdominal wall, and may resemble an acute abdomen, but the more usual signs are those of acute liver necrosis which may simulate yellow fever. Chronic poisoning resembles delayed chloroform poisoning with nephritis, oliguria, jaundice, vomiting and diarrhoa.

In ordinary anthelmintic doses the hepatic injury is not sufficient to produce noticeable effects, but toxic signs are specially noticeable when there is contamination with ethylene dichloride. Continued small doses may produce hepatic cirrhosis. Recent work indicates that the loss of ionized calcium and retention of guanidine are factors in the intoxication, interfering with normal

metabolism. Guanidine accumulates in the blood. Indications are, therefore, for a diet rich in calcium and carbohydrates, though poor in fats and proteins. Alcohol must be avoided. Where any anxiety on behalf of the patient is aroused, glucose, one drachm, frequently by the mouth or in 5 per cent. intravenous injections, is indicated. It is also useful to administer calcium lactate in full (30 gr.) doses the day before treatment to increase the calcium content. Calcium chloride is useful in controlling symptoms. Rest in bed is not absolutely essential, though advisable in enfeebled persons. The after-symptoms are drowsiness, giddiness and headache. Toxic amblyonia has been recorded.

Carbon tetrachloride acts directly on the helminths and will remove 95-99 per cent. of all Necator americanus in a single treatment, but is less effective for

A. duodenale.

The dose for an adult is 1 dr. (3.5 ml.) taken in hard gelatin-coated capsules, each containing 30 min. (1.776 ml.) of carbon tetrachloride, after a partial fast of eighteen hours without preliminary purgation. A saline purge (sodie sulph., $\frac{1}{2}$ oz.) is necessary 15–20 minutes after the drug, and an enema of hot water is usually required to empty the bowel. The treatment is best commenced at 8 a.m. and one-half of the total dose is taken after a quarter of an hour interval. The drug can be given to pregnant women, in whom oil of chenopodium is contraindicated. The minimal dose for children is 3 min. (0.2 ml.) and it should be increased by that amount for each year of age up to maturity. Many clinicians find it pleasanter and safer to give the aperient together with carbon tetrachloride, 3 ml., in castor oil, 15 ml.

It is important to note that not all the dead ancylostome worms are found in the first stool passed; they may continue to appear for three days after treatment. Similarly, the eggs of the parasite are held up in the folds of the intestinal mucosa and can be found in the fæces for at least a week after effective treatment has been completed.

- III. Trichlorethylene (CHCl: CCl₂) in doses of one drachm (3.55 ml.), which has a pleasanter taste and odour than carbon tetrachloride, is equally potent and safe, and is given the same way. On exposure to light, phosgene is apt to be generated, and this drug should always be stored in amber-tinted ampoules. If inhaled in an unrefined state, it acts as a lung irritant. The refined product, trilene, is used as an anæsthetic.
- IV. Tetrachlorethylene (C_2Cl_4) is soluble to the extent of 1 part in 10,000 of water. It is preferred to carbon tetrachloride by many, as having a pleasanter taste and being equally potent and much safer. It has been given by Soper to adults in doses of 1.6 ml. combined with 0.8 ml. of oil of chenopodium. Maplestone gave 4 ml. to men under 140 lbs. in weight. It may be given without excipient and may be mixed directly with a purgative, such as sodium sulphate. The dose for children is 2 ml. As a general rule it is dispensed in the same way as carbon tetrachloride and is subject to the same precautions.
- V. Combined treatment.—It is generally admitted that combined treatment with tetrachlorethylene and oil of chenopodium is more efficacious than the use of either drug alone. The two mix readily. The dose recommended is 2 ml. (min. 34) of tetrachlorethylene with 1 ml. (min. 17) of oil of chenopodium made up to 28·42 ml. (one fluid ounce) in liquid paraffin. The same precautions being taken, it may be given in one dose or in two halves. Tetrachlorethylene and oil of chenopodium treatment can also be given on two consecutive days. Sodium sulphate, $\frac{1}{2}$ oz. in a tumblerful of water, should be taken one hour afterwards.

The following is a practical and easily tolerated method of administering both drugs:

(1) Starve overnight.

- (2) 8.30 A.M.: 2 capsules (gelatin) of oil of chenopodium of 7.5 mins. each.
- (3) 8.45 A.M.: tetrachlorethylene, 40 mins. (Four capsules of 10 mins. each.)
- (4) 9.0 A.M.: mag. sulph. 4 drachms in water. Stools should become liquid within four to sixteen hours. If not, mag. sulph. must be repeated.

Ancylostome eggs may be passed in the fæces for six days after effective treatment. If they persist beyond this period, the course should be repeated.

It is hardly possible to get native patients into hospital for treatment, so that systems of treatment to be completed at one sitting may have to be devised, e.g., the anthelmintic may be followed in half an hour or so by a dose of salts.

VI. Hexylresorcinol, 1: 3 dihydroxy-4-hexylbenzol, is a white, waxy, crystalline substance, sparingly soluble in water, but exceedingly so in alcohol or vegetable oils. Introduced as an anthelmintic by Lawson, Ward and Brown, it is given in hard gelatin capsules or crystoids.

Give a light evening meal consisting of soft foods only, and the following morning give the dose on an empty stomach. The dosage for adults and children over twelve years of age is 5 pills; for children of eight to twelve years, 4 pills; six to eight years, 3 pills; under six years, 2 pills, 0·2 grm (3 gr.) each, with a glass of water. No food of any kind should be taken for at least four hours after treatment. Water may be taken freely, but alcohol is definitely contra-indicated. The patient may go about his usual occupation immediately after treatment and eat what he likes at the end of four or five hours. A saline purge should be given twenty-four hours after treatment to remove the dead worms. The patient may continue to pass worms for as long as ten days or two weeks after this single dose. If instructions as to food are carefully followed, one dose is usually sufficient.

Re-treatment is sometimes necessary because of re-infestation, or because the patient has not followed instructions about food. Treatment should only be repeated after two weeks, if eggs are still present in the fæces. Unlike most anthelminties, this product will successfully eliminate roundworms (Ascaris lumbricoides), hookworms and possibly also threadworms.

In crystoids the crystalline hexylrcsorcinol is gelatin-covered. If the gelatin covering becomes broken the drug may cause irritation and burning pain to oral and esophageal tissues. To avoid this, the crystoids must be swallowed whole with a glass of water; under no circumstances must the patient crush or chew them.

Convalescence.—The dieting of convalescents from serious ancylostome disease must, for a time, be very carefully conducted. A rich, full dietary is to be avoided until the powers of digestion have become re-established; otherwise, enteritis and diarrhoe may prove very troublesome and retard recovery. The anæmia responds to large doses of iron—ferrous sulphate—in doses of 24–36 gr. daily for three weeks, or even longer. Azmy and Zanaty recommend small blood transfusions, 200–300 ml., which induce an increase of polymorphonuclear leucocytes and red blood corpuscles:

In cases of severe anæmia it may be wise to give a preliminary course of iron, with a generous and balanced diet, before administering the

anthelmintic; in these cases full doses of tetrachlorethylene should be given with caution; it may be better to give a dose well below the toxic level and to repeat it as the patient becomes stronger. McFadzean and Wong (1953) insist that in Chinese patients with extreme anæmia it is better to treat the blood condition first, leaving the worms for the present in situ. Intravenous saccharated oxide at a concentration of 20 mgm. Fe per ml. (Ferrivenin) were given in doses of 50 mgm. on the first day, 100 mgm. on the second and 200 on the third and subsequent days. The ædema disappeared, enlarged cardiac shadows became normal, cardiac murmurs disappeared and previously palpable livers became impalpable. By the mouth they gave 1.5 grm. ferrous sulphate with 150 mgm. of ascostic acid in divided doses daily. The patients improved, but the hæmoglobin rose more slowly. Ferrous sulphate must be given in large doses—such as 1.3 grm. dissolved in dilute HCl with glucose and given in lemonade with 100 mgm. of ascostic acid in mass treatment of ancylostomiasis.

Assessing results of treatment.—Under ideal circumstances all stools passed after treatment should be collected, diluted with warm water, vigorously broken up and stirred, then filtered through a fine-meshed sieve (25 meshes to the inch). The defunct or stupefied worms may be picked out with forceps from the sediment. This process is facilitated by transferring it to a black photographic tray. A soft brush is used to scatter the particles. On account of their grey colour they are difficult to discern, but their recognition becomes easy with practice.

When the examination is made shortly after the stool has been passed a proportion of the worms will be found still alive and exhibiting their peculiar sinuous movements. In native cases sometimes 100–400 worms or more can be recovered, but in Europeans a bag of 70–100 is considered an exceptional figure.

The necators can be distinguished from ancylostomes macroscopically by their fine, curved heads.

Prophylaxis.— In devising a system of prophylaxis for ancylostomiasis the fact that it is by means of the fæces of the already infested that the parasite is spread must be kept prominently in view. Fæcal contamination of the soil and water must therefore be prevented. The promiscuous deposition of fæces about huts, villages, and fields must be interdicted. Tea, coffee, cocoa, banana, rubber and citrus plantations, by reason of the intensive cultivation required, are potent sources of infestation. Abundant and easily accessible latrine accommodation must be provided in coolie lines, in miners' camps, in native villages, and along the highways of traffic. The Chinese plan of storing night-soil for months in large, cemented, water-tight pits is a good one. It is known that, if the eggs of the ancylostome are kept in pure fæces, the embryo is developed and escapes in due course; but it is also known that unless the larva be supplied with a certain amount of air and earth it soon dies. The thing to be avoided, therefore, is the mixing of fresh faces with earth. Conditions of warmth, moisture and shade favour infestation, but the infective stages of ancylostome larvæ are killed in a few minutes by direct sunlight. By the Chinese system the embryos of the ancylostome larvæ are killed and, at the

same time, a valuable fertilizer is secured for the agriculturist. The presence of standing water is an advantage as it dilutes the bacterial food of the larvæ and they cannot feed in water. A rise in temperature increases activity of the larvæ, which use up the food reserves, so that in the tropics they rarely survive longer than six to eight weeks.

It is manifest that, in devising privies and sanitary regulations, the habits of the people they are intended to benefit must be taken into account; if native habits and prejudices are ignored, any system, no matter how perfect it may be in theory, will fail in practice. In America, intensive mass treatment after the installation of satisfactory latrines has been found most effective. The provision of a fool-proof latrine for natives is the chief difficulty. So far the "bored-hole" latrine, 16 ins. in diameter, has proved most acceptable. This is deep enough to prevent migration of hookworm larvæ, produces no odour and does not encourage fly breeding, but it must have a concrete or pressed steel squatting plate.

The water supply should also be carefully guarded from all possible sources of facal contamination. Drinking-water, unless above suspicion, should be boiled or strained. So far as possible, facilities for removing all earth and mud from the hands and dishes before food is taken should also be provided and their use encouraged. Badly contaminated ground had better be abandoned. The systematic periodical inspection of plantation coolies is recommended. At these inspections all subjects of anæmia or dyspepsia should be put aside for more careful examination; if the eggs of ancylostomes are found in their faces, a judicious dosing with some of the drugs mentioned may avert serious disease in the individual, and also prevent him from becoming a source of danger to his companions.

Until a few years ago, efforts at the prevention of ancylostomiasis were directed towards treating the surface of the soil, but recent work has shown that the ancylostome larve spend a considerable part of their

life in the deeper layers.

Therefore a most important factor underlying efficient prophylaxis of ancylostomiasis in a community is the life-span of the infective larva during its existence in a free state in the soil. Practical experience gained by the directing authorities in the "hookworm campaign" suggests that this is much longer than experimental evidence indicates. According to Cort, Augustine and Payne, the life of the infective larva under these conditions does not exceed six weeks, and during that time it does not wander outside a 4-in. radius in a lateral direction, but can migrate to the surface from a depth of 36 in. Baermann showed that the larvæ may be recovered with ease from soil thought to be infective; the technique consists in placing the suspected soil in a receptacle, together with a quantity of water; the larvæ then rapidly migrate into the fluid, where they can be found and recognized.

Education of children in schools by means of diagrams and instructional films plays an important part in health propaganda in the United States. In South America it is noted that, although children wear shoes at school, where the chance of infestation is not great, they commonly run barefoot at home, where infestation is likely to be acquired. Nicholls recommended common salt as a

prophylactic agent of some potency. It has the advantages of being cheap and, as a rule, easily obtainable. It has an injurious effect upon the larvæ, but requires to be brought into very intimate contact; mere sprinkling is futile. Solid salt, however, when sprinkled on fæces, does not penetrate the mass for forty-eight hours.

In view of the great danger to health that exists in certain countries from this and similar parasites, the sanitary authorities in such places ought to circulate among the people, by means of printed leaflets or posters, a few simple directions for the prevention of ancylostomiasis.

Clayton Lane estimated that out of 315 million inhabitants of India and Pakistan, 45 million wage-earners were subjects of ancylostomiasis. Employers of labour in the Darjeeling district computed that the labourer's earning capacity when freed from this disease is increased by 25–50 per cent.

An energetic and many-sided campaign against the hookworm was waged in the United States, Asia, and Africa, financed by Mr. Rockefeller. State and county dispensaries for free examination and treatment of applicants were established. The total number treated in 11 States in 1912 was 238,755. A commission worked for a number of years, and treated 393,556 people at a cost of a little over a dollar per head. reports issued by the Commission contain most valuable statistics, of which a few may be quoted. In Panama, in 1916, 30,094 persons were examined, and 80.4 per cent. found infested; of these, 98.2 per cent. received treatment and 49.9 per cent. were cured. In Antigua, of the total population, 98.8 per cent. were examined, and 29.8 per cent. found to be infested; treatment was given to 92 per cent. of the infested people, and 96 per cent. of these were cured. In British Guiana, out of 3,900 infested natives, only 8.6 per cent. remained as foci of infestation at the end of the campaign. In Ceylon, of 4,567 tea-plantation coolies, no less than 95.6 per cent. were found infested. Nevertheless, unless constant preventive measures are maintained, mass treatment is not likely to be very successful in prevention. A few infested persons may soon re-infest a population, if the old bad habits are retained.

Darling thought that, as the agricultural and mining population within the tropics is so universally infested with hookworm, the detection of individual infestations by microscopical examination was no longer necessary. The population should be treated en masse by an intensive method. The sanitarian should remember that an individual may be infested, yet not "affected" by the disease. Hence, apparently healthy persons constitute

a danger to the community.

ANCYLOSTOME DERMATITIS

A form of dermatitis affecting the feet of coolies on plantations in Assam, in the West Indies, and probably elsewhere in the tropics, is ascribed to the penetration of the skin by ancylostome larvæ, and precedes by two to four months the generalized symptoms of ancylostomiasis. The disease is of much economic importance to the planter, and is variously known as ground itch, pani-ghao (Assam), water itch, water-pox, water sores, sore feet of coolies, cow itch (Queensland), sabañones (Venezuela), candelillas (Colombia), chauffie (Grenada) and mazamorra (Porto Rico).

The soil in the neighbourhood of coolie lines is extensively contaminated by fæcal matter. The bare feet of the coolies are constantly soiled with this larva-laden earth; and in this way, in many tropical plantations, Looss's experiment is unintentionally carried out on a large scale. Dermatitis, vesiculation, and may be pustulation, or even extensive ulceration, and probably ancylostomiasis anamia, ensue. A condition resembling larva migrans (see p. 844) is often produced by allied species i.e. Ancylostoma braziliense and A. caninum of the dog. The services of the affected coolie are lost to the planter until the irritation subsides and the anamia is cured.

Fülleborn published the most complete account of this subject (1932). He pointed out that the ancylostome larvæ can only enter the skin when the soil conditions are favourable. They cannot enter through water alone, nor can they readily bore through the hard skin of the sole of the foot; they pass less easily through the tough skin of the negro than the soft epidermis of the European. It was shown by Khalil that the presence of a suitable host has no special attraction to the larvæ, but they are attracted by warmth (thermotaxis). The appearance of the skin lesions is dependent upon the number of invading larvæ. As Schüffner showed, the inboring larvæ first form a red point, and soon a small blister forms in which the larvæ can be demonstrated in sections, and the irritation of the skin is noted after some twenty minutes. Probably, the entrance of the larvæ also causes opportunities for the ingress of bacteria with formation of blebs and pustules, and this is the real "ground itch." It is by no means proven that ground itch is invariably ancylostome dermatitis, for it is not found in Egypt where this disease is rife.

Personal cleanliness and the use of some form of foot covering during the wet season, together with the prophylactic procedures for ancylostomiasis, are the special preventive measures indicated against this disease. Coolies working on irrigated land should be provided, if possible, with high, well-fitting boots. Antiseptic foot-baths and some soothing ointment are indicated. Treatment with drugs is best effected with strong salicylic solution in collodion or methyl alcohol. Barlow recommended 3 per cent. salicylic acid in ethyl alcohol.

III. CESTODIASIS

The tapeworms, Tania saginata and T. solium and their cystic forms are common enough in the tropics and subtropics, their distribution being regulated by the presence or absence of their appropriate intermediary hosts—the ox in the one case, the pig in the other—and by the habits of the population in cooking and conservancy.

The broad tapeworm (Diphyllobothrium latum) occurs in Norway, Sweden, Russia, Turkestan, Japan (where the natives eat raw fish), Lake Michigan, Madagascar, and on the shores of Lake Ngami, South

Africa.

The treatment of this tapeworm is usually successful and responds to 4 grm. of olcoresin of aspidum followed by Epsom salts. The very severe degrees of anæmia are not usually seen in the tropics in association with this parasite. Injections of liver extracts are given in after-treatment. The reticulocyte peak is reached in eight days. Dibothriocephalus anæmia has recently been shown to

be due to the absorption of large quantities of vitamin B_{12} by the parasites and it is said that when liver in dry powdered form is administered orally the anæmia is rapidly cured. Björkenheim in eighteen cases of pernicious anæmia associated with $D.\,latum$ found some presented symptoms of subacute combined degeneration of the cord.

The cestodes of man which have any claim to be regarded as special to warm climates are Hymenolepis nana, Diphyllobothrium mansoni, and Spirometra mansonioides.

TREATMENT OF TAPEWORM INFESTATIONS

General statement.—Preliminary starvation appears to be necessary for two days. On each of these sodii sulph. ½ oz., or castor oil ½ oz., should be given to clear out the bowel; the food should be restricted to weak tea, toast and unlimited amounts of lemonade and glucose D.

I. Filix-mas treatment.—Filix-mas is the rhizome of the male fern: it contains 5-8 per cent. of filicic acid (filicin), and a variable amount of aspidin; both these substances are anthelminitics.

Extractum filicis liquidum, dose 45-90 min. (2.66-5.33 ml.), has a disagreeable taste and is apt to cause vomiting, so the drug is best

prescribed in gelatin capsules.

Capsules contain 15 min. each of the liquid extract. The dose of these is one to six, according to the age of the patient. It is effective against Tconia saginata, T. solium, and especially against D. latum. The most difficult species to dislodge are T. saginata and Hymenolepis nana. On the morning of the treatment the patient should have a small cup of tea. For an adult man the full dose of filix mas is $1\frac{1}{2}$ dr., for a woman 1 dr. For specially resistant cases up to 120 minims (2 dr.) may be given with safety, as follows:—

8 a.m.: two capsules of 15 mins. of filix mas.

8.30 a.m.: repeat. 9 a.m.: repeat.

The patient must then lie perfectly quiet and take nothing but a few sips of water. At 10.30 a.m. half an ounce of sodii sulph. should be given. The bowels being opened freely by the salts, segments of the tapeworm should soon appear. All motions should be saved and strained to search for the head; should this not be seen, a soap-and-water enema should immediately be given.

The patient must rest in bed the whole day when undergoing treatment. Arteaga and Garnero have treated cases of *T. saginata* with chloroquine diphosphate (Aralen). The adult dose is one tablet (0.25 grm.) per kg. A total of eight tablets or 2 grm. in a fasting patient is followed by a large

dose of castor oil.

They report a large series of successes.

Oleoresin of aspidium (U.S.P.) contains filicin, the anhydride of filicic acid. To be successful the oleoresin should have been recently prepared. The patient should fast the day before treatment. At 6 p.m. on that

day 30 gr. of mag. sulph. are given, and again on the morning of the treatment a similar dose. No breakfast should be taken, and after the bowels have been opened \(\frac{1}{2} \) oz. of the following emulsion is administered.

An hour later a second dose of ½ oz. is given and, after a further interval of two hours, a soap-and-water enema.

None of these treatments with filix mas must be repeated oftener than once a month, otherwise toxic symptoms, such as polyneuritis and paralysis of the iris (filicic acid poisoning), may ensue.

Intraduodenal treatment of tapeworm. Sawitzky recommends giving 30 grm. sod. sulph. in the afternoon, and starving the patient for the rest of the day Next morning the bowels are opened by an enema, the patient swallows a catheter and is placed on his right side. The catheter enters the duodenum in 1-2 hours. He is then turned on his back, and a small glass funnel is attached. An emulsion of ethereal extract of male fern, 50 grm., gum arabic mucilage, 5 grm., sodium bicarbonate, 0-5 grm., distilled water, 50 ml., is prepared. About one-quarter of this amount, equivalent to 3-4 grm. (50-60 min.) male fern, is introduced; immediately 50 ml. (13 oz.) of warm 50 per cent. solution of sodium sulphate is poured in and the catheter extracted. Expulsion takes place in two hours.

II. Pelletierine—Commercial, pelletierine is a mixture of two alkaloids, pelletierine and isopelletieriene, and is obtained from the stem and root bark of the pomegranate (Puvica grandum).

Pelletierine tannate, a mixture of the tannates of the alkaloids, is a light yellow powder, slightly soluble in water (1 in 700), but soluble in 90 per cent. alcohol (1 in 80). The dose is 7 gr. dissolved in alcohol, followed two hours later by castor oil, 1 oz.; a soap-and-water enema may be necessary.

- III. Atebrin, or mepacrine, has been recommended by several observers notably Hockenga (1951) in doses of 0.8 grm. by the mouth followed by an aperient. There is a certain amount of evidence that the addition of 0.4 grm. atebrin the night before filix-mas treatment does assist in detaching the head, and successes have been recently recorded by Sodeman and Jung (1952). Milk diet on the day before and a purge of castor oil are necessary. On the morning of treatment 0.6 0.8 grm. of atebrin are given, two tablets every five minutes with water. Two to four hours later the purge is repeated and food withheld until the bowels are opened.
- IV. Hexylresorcinol has been used successfully by Morales and Stevenson in emulsion administered into the duodenum, especially in cases of T. saginata. Patients fast on the morning of treatment. A duodenal tube with a metal tube is introduced into the the stomach. The gastric contents are aspirated and the patient is turned in the right lateral decubitus position. When the duodenum is reached a mixture of 1 grm. of crystalline hexylresorcinol suspended in 30 ml. of water and containing 1 grm. acacia is introduced. When the tube has been in situ for several minutes warm water is introduced. The patient then sits up and drinks ice-water and the tube is withdrawn. Hexylresorcinol does not kill the tapeworm directly but segments are passed for four months after treatment. There are no toxic effects.

IV. Tetrachlorethylene and oil of chenopodium. Tetrachlorethylene anaesthetizes tapeworms and, especially when combined with oil of chenopodium, aids in their expulsion. It is combined in the following mixture.

This should be given in two doses, as in ancylostomiasis. Adults should receive the full dose; children under six, 2 dr.; up to eight, 3 dr.; up to fourteen, 4 dr. The mixture should be made up fresh daily. Half an hour afterwards the patient should be given a saline aperient, or *Pulv. jalap. co.* 1–2 dr. (3:55–7 ml.) may be used.

It is stated that β naphthol, gr. 15, in eachets given daily after breakfast for ten days is effective in preventing the head of the worm from forming proglettides. This treatment should be resorted to in case of failure to dislodge the head at the first treatment.

Hiyeda and Tarada discovered an active preparation in raigan—a mushroom (Omphalia lapidescens). This is given in a powdered state, in doses of 20 gr. three times daily for three days, without any preliminary preparation.

Gentian violet has been used to expel Hymenolepis nana. Halawani has had successes with chloroquine (aralen). Cusso, or Kusso, a decoction made from the flowers of Brayera anthelmintica, is said to be efficacious in Abyssinia for removing T, saginata.

Cestodin, or nematodin (Hirte, 1951), contains metallic tin and its oxide and chloride. It is given in tablet form three times on the first day, six times on the second and then three times daily for a further three days. No purgatives are given after the treatment, but a dose of magnesium sulphate before it is commenced.

IV. CYSTICERCOSIS

Though the cysticerous, or bladder-worm stage of Tania solium, normally develops in the pig, and infestation of man takes place by eating pork, which contains the larval cysticerci, yet occasionally man himself may serve as intermediate host through accidental ingestion of the eggs of T. solium. The embryos may migrate to almost any organ, especially the muscles of the limbs, tongue, neck, or ribs and sometimes the lungs, liver, or heart, and they have been removed from the eye. One of the most striking recent contributions to medicine has been the demonstration by MacArthur that the embryos show a peculiar predilection for the brain. It has been known for some time that individual cases of cysticercosis may be accompanied by epileptic seizures. Investigations on epilepsy in young and otherwise healthy British soldiers, with good antecedents, has shown that cysticercosis is the cause. In one batch of 22 cases investigated by MacArthur 10 were proved to suffer from cysticercosis. In another 82 cases in British soldiers, who had served in India, evidence of infestation with Tania solium was obtained in 22. Indigenous cysticercosis in England has been recorded. Dixon and Hargreeves, in a study of 284 cases, found that in 89 per cent. radiographic examination of the skull was negative.

In some instances the fits commence about the time the cysts are first detected; in others there may be a quiescent period of some years between the appearance of the cysts and the first epileptic seizure, or, in other instances, the cysts may

become palpable after the onset of epileptic fits. The number of palpable cysts varies widely in different cases. Large ones which have been under observation for years may vanish in a few days. The bigger cysts usually contain dead larvæ and the cyst capsule is tense, owing to the large amount of contained fluid. The death of the larvæ is in some way associated with an increase of this fluid.

Pathology.—In the brain the cysticercus becomes enclosed by a wall of neuroglia; small round cells and a few plasma cells are present between the delimiting neuroglia and the surrounding normal brain tissue, but later the tissues surrounding dead and disintegrating cysticerci undergo active degenerative changes with a marked cellular response. To the naked eye the degenerating

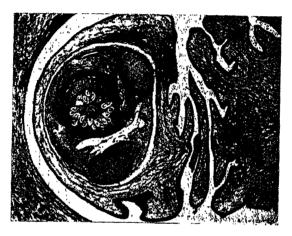


Fig. 190.—Section of cysticercus from brain. (Dr. Carnegie Dixon and Dr. J. D. Willis, Lancet, 1941.)

tissues may be visible around the cysticercus as a discoloured ring, and later, if the patient survives, they undergo necrosis. This doad area, which may extend 5 mm. beyond the cyst, is ringed off from the normal brain by a wall of sclerosed neuroglia. (Fig. 190.)

After a variable period, determined in part by the resistance of the host, the parasites die and often undergo calcareous change. Calcification commences in the scolex, while the cyst capsule and its contents are unaffected. Calcification may stop at this point, and the cyst-wall may collapse through the escape of the fluid, or the collapsed cyst may be flattened out by pressure of the surrounding muscles and calcify in an extended form. Apparently, three years elapse between death of the cysticerous and calcification in the tissues, but cysts in the brain take longer.

Symptoms.—The fits may resemble the Jacksonian type, with cyanosis, biting of tongue and involuntary passage of urine. In some instances they are irregular, and cerebral tumours may be suspected. Nervous symptoms other than fits may be produced; thus the initial clinical picture may be that of disseminated sclerosis or cerebral tumour. Psychical states may supervene with cerebral irritability and loss of memory.

Usually, the invasion of cysticerci gives rise to no general reaction, but the patient notices the gradual development of small subcutaneous or intramuscular

swellings. More rarely, a general toxemia with pyrexia develops. Sometimes, too, the localized intramuscular swellings resemble a muscular dystrophy. Cysts may be present in large numbers without the patient's knowledge until they are discovered accidentally by radiological examination. In one case the first fits commenced during treatment in hospital for T. solium, whilst Dixon and Hargreaves found evidence of previous tapeworm infestation in 26 per cent. There may be a history of incomplete fits, often regarded as hysterical, and every degree from petit mal to Jacksonian epilepsy. Intense headache may be the one symptom preceding a fatal attack. Psychical disturbances, melancholia, or acute mania may dominate the picture. Mental deterioration may be very insidious in onset, on the other hand left-sided hemiplegia of sudden onset has been recorded.

Edwards has described vague headaches with impairment of field of vision and incongruous homonymous hemianopic defects involving chiefly the lower quadrant, together with speech defects and slurring of polysyllabic words. An irritating allergic rash has also been seen.

Apparently no prophecy can be made of the duration of the epileptic symptoms. Sometimes the seizures cease without apparent cause; in others they persist for eight years or longer. MacArthur has seen one cysticercus alive in the brain after a lapse of lifteen years. There have been several fatal cases in which the cysts have been found limited to the brain.

Diagnosis.—The most helpful sign in diagnosis is the development of palpable cysts in the tissues, and these may number from one to thirty or more. They may be the size of a hard pea, a hazel-nut, or even a pigeon's egg. Their situation varies widely: they have been found in the lips, masseter muscles, neck, chest, abdominal walls, back and groin, and if not numerous they are easily overlooked. Indeed, unless evidence of cysticercosis is systematically sought, diagnosis may be missed, as nodules may be absent at the time of examination, only to come out in crops at a later date. When these external cysts are absent, as Edwards remarks, "failure to think of cysticercocis is the greatest impediment to its diagnosis." The radiological evidence may not be convincing for some years, as calcification does not usually take place for four or five years after infestation. Whilst they are alive the body is relatively tolerant, though they become active irritants when dead and calcified.

To demonstrate cysticerci, a suitable cyst is excised under local anæsthesia and the host capsule is enucleated. The appearance of the translucent membrane with its central "milk spot" is characteristic. If alive, the parasite may evaginate the head and neck, or it may be induced to do so by immersion in hot saline.

When partially calcified, a good skiagram will show it as a small elongated shadow, but the completely calcified cyst gives a characteristic appearance (Plate XXI). In showing up calcification "high penetration" is more effective than slight under-exposure. The exposure should be that ordinarily employed for bone detail. Evidence of calcification within the brain has been demonstrated. Infortunately in the early stages the cysts are diaphanous and do not show up. Therefore, a negative radiograph of the skull is of no significance. The size of the cysts depends mostly on their age and situation. Eosinophilia affords no aid to diagnosis. Complement-fixation tests have proved disappointing, and a negative test does not exclude the possibility of infestation. The intradermal Casoni test is positive in about 50 per cent. of cases. Trawinski developed a precipitin test, using an antigen made from Cysticercus cellulosæ. There may be no changes in the cerebre-spinal fluid. De Sèc and others, however, stated that excess of lymphocytes, a positive colloidal benzoin reaction and cosinophil increase, in the absence of a positive Wassermann reaction, suggest cysticercosis.

^{*}In the muscles cysticerel are oat-shaped due to pressure, whilst those in the brain are circular.

It must be remembered that the Ghedini-Weinberg complement-fixation, as well as the Casoni intradermal test, are group immunological reactions, whether hydatid extract or cysticercus fluid is used as antigen.

Treatment.—Intravenous injections of antimony tartrate have been tried, often without much effect. Although instances of successful localization and removal of single cerebral cysticereal cysts have been recorded in the literature, usually such interference is unjustifiable. Luminal and bromides are helpful in controlling fits. Observation on tissue changes which follow the death of intracerebral cysticerci suggest that destruction of large numbers of these parasites might make matters worse.

In actual practice, temporary amelioration of symptoms, after removal of

one or more cysts, has often been followed by death.

Prophylaxis.—This cannot be undertaken until the source of infestation has been ascertained. It is commonly believed that human cysticercosis is an accidental complication, auto-infection being caused by the ingestion of eggs or possibly by regurgitation of segments of *T. solium* into the stomach.

Section X.—DISEASES DUE TO POISONS, INCLUDING SNAKE-BITE, AND INFECTION WITH DIPTEROUS FLIES AND LEECHES

CHAPTER XLVIII

VEGETABLE POISONS

POISONS USED FOR CRIMINAL PURPOSES

THE inorganic poison most generally used by tropical races is arsenic in some form, eleverly intermingled, as a rule, with flour, inserted into the grains of maize or millet, or introduced into sweets, as in Egypt; in Malay, powdered croton seeds or datura are used. Natives usually possess a much wider and more intimate knowledge of organic poisons than do civilized peoples.

In Brazil, common native poisons are derived from Paullinia pinnata, which contains an alkaloid, timboin, and from the fruit of Thevelia ahonai, the active principle of which is thevelosin; both of these cause vomiting and respiratory failure.

In Indonesia a poison extracted from the roots of Milletia sericea produces debility, headache, diarrhoa, collapse and death.

In the Pacific islands the native poison is derived from the fruit of Barringtonia speciosa.

In India a large number of vegetable poisons are in use. In the Madras and Bombay Presidencies an extract is obtained from the roots of Nerium odorum, the white cleander, which contains two glucosides exerting a specific action on the heart. Similar substances, urechitin and urechitoxin, from Urechites suberecta, exert a cumulative action, and therefore sudden death may be produced without

arousing suspicion of poisoning.

The jujec of an Asclepias (or milkweed) is used in India as an infanticide: the symptoms are vomiting, salivation and cramps. The roots of various species of aconite (Aconitum ferox, etc.) are used for the same purpose; death takes place rapidly—in three to six hours, as a rule. Several species of Apocynaceæ, such as Cerbera odollam and Thevetia neriifolia, the sap and seeds of which contain a glucoside, thevetin, are very deadly, death from cardiac failure taking place in twelve to fifteen hours. In Southern India, Burma, and Ceylon a decoction of the fruit of Cloriosa superba, one of the Liliaceæ, allied to squill, is employed for criminal and suicidal purposes. The active principle, superbin, causes gastrointestinal irritation and cardiac failure within four hours. The commonest poison in India and Ceylon is datura, one of the deadly nightshades, of which there are several species. The seeds, mixed with food or drink, produce a state of extreme mental exaltation, followed by coma; the active principles are atropine, hyoscyumine, and scopolamine.

In Africa the leaves of Hyoscyamus fahezlez, containing hyoscyamine and scopolamine, as active principles, are used by Tuaregs of the Sahara. On the West Coast of Africa, a decoction of a cactus, colloquially known as "oro," produces blisters in the mouth, vomiting and gastro-intestinal irritation, collapse and death. In China, opium is the suicidal poison most frequently used,

especially by women.

DISEASES DUE TO THE INGESTION OF POISONOUS FOODS AND WATER

LATHYRISM AND FAVISM

This disease, characterized by various nervous manifestations, such as ataxy, spastic paraplegia, weakness and muscular pains, without psychical disturbances, occurs in Abyssinia, Algeria and India in those districts in which vetches. "Khasari," Lathyrus sativus and allied species, form the main article of diet. Howard and his colleagues (1923) demonstrated that the wild vetch (Vicia sativa). which contaminates this crop, is harmless, but that the poison is contained in a variety, var. angustifolia, which contains alkaloids: vicine and divicine. There are two varieties of L. sativa: the larger called lakh or teova: the smaller lakhori or teovi. Rudra (1952) considers that the toxic principle is selenium. methionine excretion is diminished. A similar disease occurs in animals fed upon the same food. The arms and trunk are seldom involved; incontinence of urine and sexual impotence are early and common symptoms. The disease is very chronic and seldom ends fatally. Shah (1939) claimed that cases improve rapidly on dietetic and vitamin treatment, and Anderson (1939) suggested that elements of the vitamin A complex are involved and that they are effective in treatment. Rudra advises the administration of methionine.

Favism, an allergic manifestation, due to a bean (Vicia fava), produces a syndrome resembling blackwater fever and is common in Sardinia, Greece and

the Mediterranean area (see p. 64).

ATRIPLICISM

A combination of cutaneous and nervous symptoms in China is caused by eating leaves of Atriplex littoralis. The earliest symptoms consist of itching of the hands, followed by ædema, and often by bullæ; the finger-tips may become gangrenous, cutaneous hæmorrhages may occur, and the face and cyclids become cyanotic and ædematous. In many aspects it resembles Raynaud's disease and crythromelalgia. Yu Ky described a syndrome after eating the leaves of Atriplex servata, or Chenopodium hybridum, in which the symptoms and signs are similar, and it is thought that the skin lesions can be ascribed to light-sensitive dermatosis.

ACKEE POISONING (VOMITING SICKNESS OF JAMAICA)

An acute and fatal condition, locally termed "the vomiting sickness," has been known for many years in Jamaica. It is found principally in rural districts in circumscribed epidemics. The causation and nature were neither apprehended nor understood, although several Commissions had attempted to elucidate them. To Sir Harold Scott belongs the merit of clearing up this mystery, and of indicating simple and practical methods of prevention, which have saved the lives of many children. It is estimated that since 1886 over 5,000 lives have been lost in Jamaica from this cause.

Vomiting sickness is confined to the West India Islands, practically to Jamaica,

and occurs principally in the cooler months, from November to April.

Symptoms.—A previously healthy child suddenly complains of abdominal discomfort, vomits several times, recovers, and perhaps falls asleep. Three or four hours later, vomiting—now of a cerebral type—returns. Within a few minutes, convulsions and coma supervene, and death follows, on an average, about twelve hours from the initial vomiting, though it may take place in one and a half hours. The case-mortality amounts to 80–90 per cent. In those who recover, convalescence is complete in twenty-four hours.

During the attack the temperature is normal or subnormal, rarely rising to 101° F.; the pulse rate is 90 to 100; the respirations are 26 to 30, sometimes,

as death approaches, of Cheyne-Stokes type. The pupils are slightly dilated and, until near the end, react to light. Except during the convulsive seizures, there is no muscular rigidity. Post-mortem examination reveals hyperæmia of viscera with a tendency to minute intestinal hæmorrhages, together with marked fatty changes, especially in the liver and kidneys, and sometimes in the pancreas and heart-muscles.

Ætiology.—Scott showed, on what must be regarded as convincing evidence—clinical, seasonal, epidemiological, and experimental—that vomiting sickness is the result of poisoning by a fruit, much used by negroes in Jamaica, called ackee, the fruit of Blighia supida (Fig. 191), a tree very common in the island. A similar species is found on the West Coast of Africa, where it is known as Irsin. When mature and in good condition, this fruit is wholesome enough; if gathered, before it is quite ripe and before it has opened while on the tree, or if gathered from an injured branch, or opened after falling to the ground, it is poisonous. The poisonous element in the immature and unsound fruit appears to be soluble in water, for "pot water" in which the ackees have been cooked is much more toxic than cooked fruit. The poison is precipitated by alcohol. Jordan and Burrows showed that the toxic principle is also contained in the seeds and in the arilli of the ackee which have not yet "opened." Evans and Arnold (1938) isolated suponin, which appears to be the toxic agent.

Treatment. An emetic, and washing out the stomach with an alcoholic fluid

during the primary vomiting, are indicated. Scott is insistent that administration of alcohol must be prompt.

Prophylaxis. When the fruit in various stages falls to the ground, only the opened pods, that is the ripe fruit, should be used for food. The immature unopened pods should be destroyed.

MANIOC AND NAMI POISONING

Manihot aipi (sweet cassava) and Manihot utilissima (bitter cassava) are ground roots extensively used in the West Indies. From the latter are produced starch, tapioca, and cassava cakes. Poisoning arises from failure to remove the



Fig. 191.—Ackee fruit. Blighia sapida. 1 nat. size. (After Byam and Archibald.)

contained glucoside and enzyme. In the presence of water these release free hydrocyanic acid, so that nausea, vomiting, distension of the abdomen and impeded respiration result.

Nami (Dioscorea hispida, Dennst, and D. hirsuta, Bl.) is a colloquial term for a species of yam, employed for food in parts of the Philippines. It has frequently caused food poisoning, and occasionally it has been put to criminal purposes. An alkaloid—dioscorine—has been obtained from the full-grown tubers.

CORAL PLANT (Jatropha multifida, L.)

Coral-plant poisoning was reported by Raymond from Tanganyika, the symptoms being colic, cramps and thirst, with subnormal temperature. Two

species, J. curcas and J. glandulifera, are common in the West Indies. J. glandulifera, since it grows rapidly, is used in Jamaica for fencing enclosures. The nuts taste like sweet almonds, and the plants are known as "physic nuts"; a third species, J. mullifida, is known as the "French physic nut." J. gossypifolia; which occurs in the West Indies, is known as the wild cassava, or "belly-ache bush," and its seeds contain an intestinal irritant like croton oil. A fifth species, J. urens, from the same area, bears leaves provided with stinging hairs, which cause itching, smarting, flushing of the face, swelling of the lips and faintness. Recovery is rapid after ejection of the poison by vomiting.

GINGER PARALYSIS (Jake paralysis)

This is a flaccid paralysis of the distal muscles of the limbs without involvement of sensory nerves. The arms are affected later. The deep reflexes, especially the knee-jerks, are exaggerated. Deaths have been recorded from respiratory paralysis in South Carolina and Tennessee from eating Jamaica ginger adulterated with triorthocresyl phosphate.

JENGHOL POISONING

Jenghol poisoning (Djenkol) occurs in Java from eating a bean, *Pithecolobium lobatum*, or *D. geminum*, and was described by de Langen, Hijman and Van Veen. The symptoms are chiefly pain in the renal region, dysuria, and often anuria. The urine frequently contains blood-casts and sharp acid crystals of jengcolic acid. The presence of these crystals in large numbers in the urethra causes



Fig. 192. Hippomane mancinella, fruit and inflorescence. (After K. V. Earle.)

necrosis, fistula and extravasation. The jenghol bean has a high vitamin-B content and is used as food in spite of its toxic properties. The beans are buried in the ground for ten days and eaten when they begin to sprout. Ingestion of these beans by normal persons is followed by an increase in excretion of sulphur.

DATURA POISONING

Various plants belonging to the order Solanaceæ are used in many parts of the tropical world to produce unconsciousness. The seeds of Datura fastuosa are used by Thugs in India for this purpose, but datura poisoning is by no means confined to India. The seeds have a slight taste and are consequently easily introduced into food; their intoxicating properties are widely known. D. sanguinea is used in Peru and Colombia, D. ferox and D. arborea in Brazil. The

characteristic seeds are found in the fæces and, in fatal cases, in the small intestine.

MANCHINEEL POISONING

The manchineel, or manchineale, *Hippomane mancinella*, belonging to the order Euphorbiaciæ, is a tree thirty to fifty feet high and of a circumference of five to ten feet, distributed along the coastline of North, South and Central America and the West Indies. It is particularly common in Barbados, Grenadine Islands, and the Archipelago of Les Saintes, in French West Indies. Two varieties are recognized, one with "holly" and the other with "laurel" leaves; both are equally toxic. The first, which resembles a crab-apple, has a pleasant odour. (Fig. 192.)

The latex contains a greenish resin, which is the active toxic principle. Like the Upas tree, the manchineel has been said to bring death to those who sleep under its shade. All parts of the tree are toxic, but the amount of latex in any portion varies with the season; even the dry wood and sawdust are endowed with irritant properties. Hypersensitive people who pick manchineel apples (or fruit) may suffer from a skin cruption with crythema, bullæ and vesiculation. Toxic dermatitis is especially likely to affect the genitalia and the anus, causing a vesiculo-pustular cruption which may be confined to the corona penis. Conjunctivitis with pain, photophobia and blepharospasm may result from the introduction of the latex into the conjunctival sac. Severe dermatitis brought about by handling dried wood-powder is thought to be allergic.

If the fruit is eaten, as it may be by ignorant visitors, children or insane people, vesiculation of the buccal mucous membrane with diarrhee and blood-and-

mucus stools may ensue. Fatal poisoning may result.

Manchineel juice on the skin should be washed off with sea-water. Blisters should be kept aseptic, and, if extensive, should be treated like a second-degree burn. When the fruit has been eaten, emesis should be induced.

ALCOHOLISM AND DRUG HABITS

Alcohol poisoning occurs in varying degrees among nearly all native races, and in symptoms and course does not differ materially from alcoholism in other parts of the world. Rum (65–72 per cent. of alcohol), obtained from the fermentation of molasses, is used in the West Indies and South America; arrack (50–60 per cent. alcohol) is manufactured in India, China, and Java from fermented rice or from palm sap; while a slightly fermented drink, toddy, is obtained from sweet sap of various palms, and is drunk in India, Ceylon, and West Africa. In South America a potent alcoholic drink is made from the fermented juice of Agave americana, and is known as "pulque."

Opium poisoning.—The opium habit, either eating or smoking—the symptoms of which are too well known to require description—is common throughout the tropics. Opium poisoning is also a favourite form of suicide, especially among women.

Cannabis indica.—Indian hemp, or hasheesh, grows in India, Persia and Arabia, and is a variety of the common hemp, Cannabis sativa. The leaves are powdered down, and either chewed or smoked in a preparation known as bhang; an extract of the flowers is known as ganga. Both these preparations cause great nervous excitement and, if persistently used, often lead to permanent insanity, the main features of which are hallucinations and illusions. Hasheesh, in various preparations, often with the addition of extracts of various Solanacese, such as datura and nux vomica, is habitually taken daily by millions of the inhabitants of Africa and Asia. The most stringent Government regulations have been framed to suppress trade in this drug.

Kawa, or yangona, the powdered root of one of the Piperaceæ, prepared to form a beverage, is drunk on festive occasions throughout Polynesia. Formerly the root was masticated by specially selected girls in the preparation of the drink, a practice which was then a prolific source of tuberculosis. Over-indulgence in kawa induces a state of hyperexcitement, with loss of power in the legs. Chronic intoxication produces debility, with coarse roughened skin.

Betel.—Chewing betel, the leaves of *Piper betel*, together with lime and areca nut (*Areca catechu*), is a common practice in India and Ceylon, and generally throughout the East. The mouth, lips and teeth are stained a bright-red colour. It produces a flushing of the face, and has mild stimulant and possibly anthelmintic properties. In Central Africa the nuts of the kola tree (*Sterculia sp.*) are chewed habitually, and act, like betel, as a stimulant, without, it is said, producing any detrimental effects.

Cocaine (Erythroxolon cocoa) is widely used in India and in parts of South America as a stimulant and intoxicant. The leaves, first dried in the sun, are chewed with lime or, as in India, with betel. This drug produces a loss of sensation in tongue and lips, the pulse is accelerated and there ensues a period of hilarity and exaltation. The drug addict soon becomes emaciated and cachectic.

MUSHROOM POISONING

There are many poisonous species of mushroom, particularly the genus Amanita in Southern Europe and U.S.A., more especially A. phalloides, the "death cap." These mushrooms cannot be distinguished by their taste and are said to possess an agreeable flavour. They can be recognized by persistence of a portion of the veil encircling the stem a little below the cup. A. muscaria contains an alkaloid, muscarine, which is allied to pilocarpine. Atropine constitutes an efficient antidote.

FLAX DARNEL (Lolium linicolum or L. temulentum) Poisoning

Brinton (1946) has described recurrent epidemics of food poisoning in the native population of Aden due to Ethiopian wheat containing this poisonous weed, known in local Arabic as *Miscara* ("tipsy"). Each weed seed is covered by a mould known as *temuline*. Within a quarter of an hour the patient becomes dizzy, with headache, slurred speech and generalized tremors and staggering gait. Sometimes there is diarrhea, nausea and abdominal pain. Stupor and coma supervene and last for about ten hours. This state is known as "Lolism" and is common in Ethiopia.

CATHA EDULIS OR MIRAA POISONING

Miraa is a local name (muiragi, khat, cafta) of a tree, *C. edulis*, about 20 ft. in height, indigenous to Africa. The leaves or twigs may be chewed or infused to make "Bushman's tea," or may even be smoked, when it induces a happy mellow sense of friendliness. Carothers (1945) describes cases of mental disturbance in addicts. *C. edulis* contains three alkaloids, *cathine*, *cathinine* and *cathidine*. Except that it is not an analgesic the action resembles that of cocaine.

EPIDEMIC DROPSY

Synonym.—Argemone Oil Poisoning.

Definition.—Epidemic dropsy somewhat resembles beriberi. Clinically, it is characterized by dropsy associated with cardiac symptoms, but without paralysis or anæsthesia.

History and geographical distribution.—This condition was first noted in Calcutta in 1877; it has since occurred there sporadically, but vanishes in the hot season. In Mauritius, in 1879, it affected one-tenth of the coolies, of whom a large number died. An epidemic broke out in Fiji in 1926 and was limited to Asiatics; no native Fijians were affected. In Purulia (Nagpur, India) there have been epidemics at intervals since 1913, the worst being in 1934 when over 2,000 were attacked. Meaker (1949) has described an outbreak in coloured labourers in N.W. Cape District.

Ætiology.—In spite of the apparently wide distribution of this disease, most of the information comes from India, where this form of poisoning is especially seen in the Hindus, particularly in females. Children under puberty are less liable than adults; sucklings are seldom affected. The weak and the robust are equally susceptible. It has been remarked that very few are of the poorer class, nearly all coming from the middle and upper classes.

The outbreak in Fiji in 1926 was attributed to mustard oil used in the preparation of curries, and later, Banerji and Ghosh in Bengal came to the same conclusion. The Mexican poppy, Argemone mexicana, is a common weed in India as well as in Australia, where it is usually mixed with wheat and fed to fowls. In them it produces changes in the comb, paralysis of legs and ædema of wattles and subcutaneous tissues reminiscent of epidemic dropsy in man. Bhattacherjee was the first to bring forward evidence that oil from the seeds of this poppy was responsible for toxic manifestations in man. Later, Pasricha showed that the toxicity of contaminated mustard oil could be eliminated by heating to 240° C. for fifteen minutes. Lal and his colleagues found that the seeds of A. mexicana (Sialkanta in Hindu) are present in many stocks of mustard seed in India, used in the preparation of Katakar oil for cooking. Cullinan (1947) described an outbreak amongst African troops in Madagascar which appeared to be due to fungus-infected rice. Sanguinerine is believed to be the toxic principle of argemone oil. In animal experiment it has been found to cause capillary dilatation and interferes with oxidation of pyruvic acid.

The atiology now appears clear. Argemone oil, under experimental conditions, produces symptoms indistinguishable from those of "epidemic dropsy." It can be detected by a simple colour test, on adding nitric acid to contaminated mustard oil. Sarkar did not consider that this is sufficiently delicate, but stated that argemone oil, when heated with ferric chloride in the presence of strong hydrochloric acid and ethyl alcohol, gives an orange-red precipitate. Two ml. of the oil to be tested are taken in a test-tube, 2 ml. of concentrated hydrochloric acid are added, mixed and heated in a water-bath at 92-95° F. for two minutes. Then 0.8 ml. of ethyl alcohol is added, the mixture shaken thoroughly and kept in a water-bath for one minute. Two ml. of ferric chloride solution are then run in, the contents mixed thoroughly by shaking, and the whole heated in a water-bath for another 10 minutes.

Pathology.—De described as characteristic extensive vascular dilatation in the deeper layers of the skin. The heart-muscle shows no degenerative changes, but there is thinning of the muscle-walls, and muscle fibres are separated by dilated capillaries; similar changes are present in the ciliary body of the eye, leading to excess of fluid in the anterior chamber. Shanks also found capillary dilatation wherever the vessels are least supported, and this is most obvious in fatty tissues, whether subcutaneous, subpericardial or subperitoneal. Similar changes are seen in the lungs, in the cervix uteri, in the ovaries and in the intestines. The liver usually presents a "nutmeg" appearance (Shaha). In Fiji vascular outgrowths resembled sarcoids and bled profusely. The chief changes occur in the blood-vessels, which are dilated and surrounded by proliferating endothelial cells.

Chatterjee and Halder found that in an average case the total erythrocyte count is about 3.8 millions, whilst the hæmoglobin is reduced to 11 grm. per 100 ml. The lymphocyte percentage is raised and there is usually considerable eosinophilia. The reticulocytes are not increased as a rule.

Symptoms.—Dropsy is almost invariably present. It usually appears first in the legs, and in some instances is confined to them; in others it involves the entire body. Occasionally, it is very persistent, recurring during convalescence. Fever also is very constant; sometimes it precedes, sometimes it accompanies, sometimes it follows the dropsy. It is rarely high, ranging usually from 99° to 102° F. Diarrhœa and vomiting generally ushered in the disease in the Mauritius epidemic. In Calcutta these symptoms were not so frequent, although by no means rare, occurring at both earlier and later stages. The total duration is about six weeks. An outbreak in the employees of the E. Indian railway

was reported by Goel in 1945. There were 476 cases. The largest proportion were exdematous and a considerable number had diarrheea and pyrexia. Edema of feet and legs lasted for two weeks. There was patchy pigmentation over nose, malar bones and shins. Tachycardia was common and mortality 4.4 per cent.

Peripheral neuritis is absent and the knee-jerk is not abolished, but usually distressing aching of muscles, bones and joints is prominent. An exanthem, erythematous on the face, rubeolar on the trunk and limbs, was frequently seen in Mauritius, less so in Calcutta. It appeared about a week after the cedema, and lasted from ten to twelve days. On the skin, vascular nævi often appear



Fig. 193.—Nodular lesions (sarcoids) in epidemic dropsy. (After De and Chatterjee.)

and may bleed profusely, while telangicctases are common. De and Chatterjee described the eruptions as "nodular," resembling sarcoids, in some epidemics, while lesions on the mucous membranes have been noted. They do not inconvenience the patient, but may bleed uncontrollably. Ecchymotic patches consist, not of hæmorrhage, but of telangicctases. Three to six weeks after the first symptoms, nodular excrescences are seen; there may be 100 or more; they may be sessile or pedunculated, varying in size from a pea to a lemon, and they bleed readily (Fig. 193).

Disturbances of the heart and circulation are prominent in nearly all the cases. The pulse is weak, rapid and irregular, the blood-pressure low; cardiac bruits are often noted. Breathlessness on exertion occurred in all cases, severe orthopness in many. Signs of pleural and pericardial effusion, of cedema of

the lungs, of pneumonia, and of cardiac dilatation are common. Hawes stated that the lung signs are characteristic and resemble a bronchial spasm with defective aëration. Anæmia is usually marked, and so are wasting and prostration. The urine is not albuminous, but of low specific gravity and greatly increased in amount. Concurrent glaucoma is not uncommon (Kirwan).

Diagnosis.—It may be necessary to differentiate epidemic dropsy from the war ædema as observed in Central Europe and Egypt during the 1914–1918 and 1939–1945 wars. The latter occurred in a population undergoing dietetic restrictions, and was characterized by great emaciation and a high degree of anæmia. Experiments with rats fed on diets deficient in proteins and salts produce a condition not unlike nutritional ædema. From ædematous beriberi the disease is differentiated by pyrexia, the peculiar erythematous rash, and persistence of the deep reflexes. A history of family outbreaks following the use of mustard oil suggests epidemic dropsy. Not all batches of oil are contaminated with argemone oil.

Treatment is based upon the facts: (1) the adulterant argemone oil is the primary cause; (2) that it is a cumulative poison; (3) that it causes capillary dilatation and permeability; (4) the serum albumin and calcium are reduced, whilst serum globulin is increased; (5) carbohydrate metabolism is checked at the pyruvic acid stage; (6) myocardial damage is set up. Antihistaminic drugs such as phenergan benefit though no rise in blood histamine has been demonstrated. Restoration of damaged capillaries by vitamins C, E and P, protection of the liver by a diet rich in protein and fat with glucose and insulin (10 units twice daily) is indicated. The calcium deficiency is restored by 10 per cent. calcium sandoz intravenously.

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CHAPTER XLIX

ANIMAL POISONS

Poisonous Snakes

SNAKES form a sub-order of the reptiles and have definite characters. The quadrate bone is articulated to the skull, but there is no tympanic cavity. The brain-capsule is osseous, and the mandibles are united mesially by a highly elastic ligament. The limb girdles are absent or reduced to mere vestiges. A peculiar feature is that there are no movable eyelids, but the eyes are covered with a transparent disc, which is shed with the rest of the epidermis. The tongue is deeply bilid and is retractile

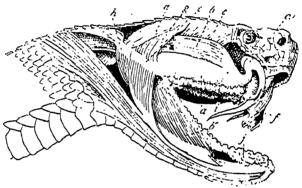


Fig. 194.—Poison apparatus, venom gland, and muscles of rattlesnake (lateral view).
(After Duvernoy, in Bonlenger's "Snakes of Europe.")

a, Venom-gland; a', venom-duct; b, anterior temporal muscle; b', mandibular portion of same; c, posterior temporal muscle; d, digastricus muscle; c, posterior ligament of gland; f, sheath of fung; g, middle temporal muscle; h, external prerygoid muscle; i, maxillary salivary gland; f, mandibular salivary gland;

into a basal sheath; but is protrusible when the mouth is closed through a notch in the rostral shield. As in the lizards, the anal cleft is transverse.

Characters used for identification and classification.—Osteological and dental characters are employed to determine families and genera, and it is therefore necessary to understand the various types of ophidian skulls and the different arrangement of fangs and solid teeth. For generic and specific distinctions the form and number of the epidermal shields and scales are of great importance.

The arrangement of the scales on the head is shown in Fig. 195, and that of the prefrontal and preocular scales varies in different species and genera. In the crotaline, or pit vipers, there is a sensory uveal pit situated between the eye and the nostril. Viperine snakes can generally be distinguished from the colubrine by their smaller size, the angular shape of the head, and the sharp stumpy tail. The maxille are vertically erectile, with enormously enlarged tubular fangs situated anteriorly (Fig. 196).

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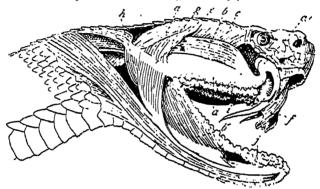


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The poison apparatus consists of a pair of venom-secreting glands connected by ducts to the poison-fangs in the maxillæ; they are analogous

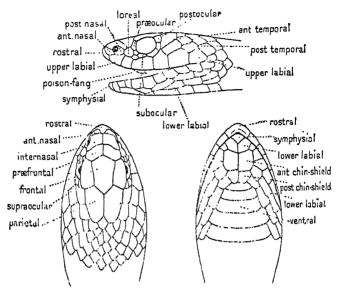


Fig. 195.—Head-shields of Causus rhombeatus. (After Boulenger, "Proc. Zool. Soc." 1915.)

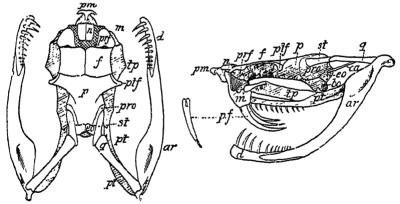


Fig. 196.—Skull of Trimeresurus gramineus, upper view and side view. (After Boulenger, "Vertebrate Fauna of the Malay Peninsula; Reptilia and Batrachia.")

ur, Articular; ho, basicceipital; ca, columella auris; d, dentary; eo, exoccipital; f, frontal; m, maxillary; n, masal; p, parietal; pf, poison-fang; pm, promaxillary; prf, prafrontal; pro, probtle; pt, ptorygold; ptf, postfrontal; q, quadrate; st, supratemporal; tp, transpalatine.

to the parotid glands in mammals. These glands, situated in the temporal regions, are operated during the act of biting, when they are squeezed by

the contraction of the temporal muscle, the venom being expelled by means of the grooved or tubular fangs. (Fig. 194.) In the African "spitting cobras" the venom is ejected with great force into the face of the enemy.

In striking, the snake throws itself forward with great violence. On the whole vipers strike with greater velocity than colubrines. Most strike with the jaws closed, but as the head approaches the victim, the mandibles are depressed by rapid contraction of the digastric and other muscles and simultaneously the fangs are elevated and rotated forward. The fangs of colubrines are grooved and shorter than those of vipers. Closure of the jaw is brought about by the simultaneous contraction of the temporal muscles which strongly elevate the mandible (Fig. 197). In

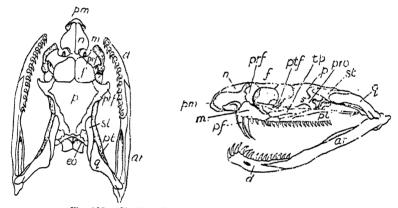


Fig. 197.—Skull of Naja naja, upper view and side view. (After Boulenger, "Catalogue of Snakes," vol. iii.)

ar, Articular; d_i dentary; co_i exoccipital; f_i frontal; m_i maxillary; n_i masal; p_i parietal; pf_i poisonfang; pm_i premaxillary; prf_i prefrontal; pro_i proöfie; pt_i pterygold; ptf_i postfrontal; q_i quadrate; st_i supratemporal; tp_i transpalatine.

vipers, expulsion of the venom is instantaneous, and independent of fixation of the lower jaw. Immediately after the insertion of the fangs and accompanying discharge of venom, contraction of the retractor muscles drags the elevated fangs downwards and backwards through the tissues. Impression of the fangs and the pterygo-palatine indentations may be made in Kerr's impression compound of dental wax, and by this method it has been found that the distance between the fang punctures affords a fair index to the venom-yield. Death may follow inoculation from a single fang (Fairley).

The lethal dose of venom varies within wide limits when tested on different species of animals. The killing capacity of different venoms for sheep, estimated in terms of average venom-yield, was found by Fairley to be: 118 for the Australian tiger snake (Noteclis scutatus), 31.7 for the cobra, 2.2 for Russell's viper, 84.7 for the Australian death-adder (Acanthopis antarcticus), 8.9 for the copperhead (Denisonia superba), and 1.5 for the black snake (Pseudechis porphuriacus).

The renom, a clear, amber-coloured fluid, is composed of modified proteins. It is of two kinds; that of the Viperidæ (vipers) acts principally upon the vascular system, but that of the Colubrinæ, Elapinæ and Hydrophinæ, i.e. cobras and sea-snakes, acts upon the nervous system and brings about respiratory paralysis. The specific action of venoms appears to depend upon the ferments and lysins they contain. As far as is known, the following substances enter into their composition: fibrin ferments; proteolytic ferments; cytolysins acting upon red cells, leucocytes, epithelial and nerve cells; agglutinins; and neurotoxins with affinity for all nervous tissue, especially for the respiratory and vasomotor centres. It was shown by Pepew that the addition of 0.4 per cent. formol (10 per cent. formaldehyde) to snake venom, and its maintenance at 38° C., transform it into anavenin (analogous to anatoxin in diphtheria).

Witts and Hobson confirmed the observation of Trevan and Macfarlane that the congulant action of Russell viper venom on blood and plasma can be enhanced by addition of lecithin. Leathes, Mellanby, and later Pratt, showed that the venom acts as a thrombokinase, converting prothrombin into thrombin, in the presence of calcium, and that lecithin acts as an adjuvant.

Several medicinal uses for snake venom have been suggested, and it appears from the work of Macfarlane and Burgess Barnett that the venom of Russell's viper acts as a certain styptic in hamophilia. One drop of a 1 in 1,000 solution of the venom, when added to ten drops of hæmophilic blood, caused clotting in seventeen seconds, although without venom this took thirty-five minutes. In a normal person hemorrhage from a toothsocket or tonsil-bed, or capillary oozing into an abdominal wound is controlled instantaneously. In hamophilic patients with bleeding toothsockets, hamorrhage ceases when the wound is lightly plugged with gauze soaked in venom 1 in 10,000, but, as Cambrook pointed out, for dental purposes the venom is unstable unless kept in an ice-chest. Cobra venom also possesses analgesic properties, and has been employed for the relief of pain, for which purpose the dried scales of the venom are dissolved in physiological saline in glass ampoules. Usually 2 or 3 units are first given to test whether the patient has an idiosyncrasy to the toxin, and then 5 units are injected intramuscularly, to be repeated daily if marked relief from pain is obtained. This venom has also been employed in the treatment of epilopsy, but results are so far inconclusive.

Symptoms of snake-bite in man.—The physiological action and symptoms produced by snake venoms can be classified into two groups, colubrine and viperine.

1. Colubrine.—In cobra-bite (Fig. 198) (Naja naja) there is severe pain and the part becomes inflamed and codematous. After an hour the patient becomes dull, apathetic, and unable to stand. Nausea and vomiting, with profuse salivation and paralysis of the tongue or larynx, supervene. Soon, the respiratory centre becomes involved, and respiration ceases entirely. Should the patient survive the paralysis, recovery is rapid. The pupil is contracted throughout. The king cobra, or hamadryad (Naja bungarus), is the most formidable and aggressive of all the cobras.

The bite of the krait (Bungarus fasciatus, Fig. 199) is extremely dangerous, especially in Northern India; the symptoms are similar to those produced by the cobra. Dendraspis viridis, a very agile and aggressive species, is regarded as the most dangerous of African snakes.

The symptoms caused by the bite of the Australian colubrines may not be very severe, but constitutional effects appear with great rapidity—sometimes in as short a period as tifteen minutes. A feeling of faintness and irresistible desire to sleep are soon followed by paresis of both legs, vomiting and cardiac paralysis. The pupil is widely dilated and insensitive to light. Should the patient survive the coma, recovery is complete and no sequelae occur.



Fig. 199.—The krait (Bungarus fasciatus).

Fig. 200. The daboia (Vipera russellii).

2. Viperine.—For the type of lesion produced by the viperines, that of Russell's viper, the daboia (Vipera russellii, Fig. 200) may be taken as an example. This species is extremely deadly; the bite causes severe pain with rapid and extensive orderna, together with blood-stained discharge, and ecchymoses around the site of the punctures. Collapse, small thready pulse, nausea and vomiting, and dilated, insensitive pupils, soon supervene, together with a loss of consciousness, more or less complete, from which temporary recovery sometimes occurs. Should the effects of the now diffused toxin wear off, the local condition of the wound becomes aggravated; extensive suppuration and sloughing, malignant codema, or even tetanus and hamorrhages from the mucous surfaces—hematuria or melæna—may supervene. There is no paralysis of the muscles, but Rogers showed that viperine toxin produces vasomotor paralysis. It is more easily destroyed by caustic agents than colubrine venom.

The bite of *Eclus carinatus* (Fig. 201) is less dangerous than that of the daboia, but is in many ways similar in its effects.

The bites of the rattlesnakes—Trimeresurus and Crotalus (Figs. 202, 208)—are remarkable for the local disturbance they produce. Constitutional paralytic symptoms come on quickly, usually in less than fifteen minutes. Should the patient recover, swelling and discoloration extend up the limb and trunk, and general symptoms of blood-poisoning with pyrexia, restlessness and delirium set in. The wound suppurates freely and may become hæmorrhagic, or even gangrenous.

The symptoms produced by the bite of the European vipers resemble those of *Crotalus*, but are very much milder.

The mortality from snake-bite, even of the most venomous varieties, is not so great as is popularly supposed, and is estimated at about 30 per cent. That it is not more is probably due to the fact that the reptile is seldom able to inject a full dose of venom. If given a fair chance, the cobra is able to inject the equivalent of twenty lethal doses at a time.

Treatment.—To be effective, all treatment should be vigorous and prompt. It should be directed, first, to prevent absorption of the poison; secondly, to neutralize, as far as possible, its toxic effects. A ligature should be tied around the limb, immediately above the bite; for this purpose, if it is at hand, a stout india-rubber band, firmly applied, is the best ligature, or strips of clothing may be loosely knotted round the limb



Fig. 201. -The phoosa (Echis carinatus).



Fig. 202.-- Rattlesnake (Trimeresurus lanceolatus).



Fig. 203.—Rattlesnake (Crotalus terrificus).

and subsequently tightened by twisting with a stick. It has been shown that by local renescetion one-half to one-third of the injection venom can be removed. A second ligature, tight enough to obstruct the return of the venom, but not the arterial circulation, is applied immediately distal to the arterial ligature. An incision is made into one of the veins draining the bitten area, and a series of blood-lettings carried out by loosening the arterial ligature whilst leaving the venous one in position. This probably has little or no effect in preventing the absorption of the neurotoxins of the colubrines, but it is no doubt very effective in localizing the fibrin ferments of the viperines, causing extensive intravascular clotting in the bitten part, preventing the process from becoming generalized, and affording time for the action of remedies.

Mole and Everard (1947), in the treatment of the bites of *Echis carinatus*, advocate that the bitten part should be elevated and cooled to reduce circulation. Continued blood transfusion is deemed necessary to maintain blood volume, despite loss of fluid and blood. A high urinary output should be induced by fluids given by the mouth and intravenously, thereby accelerating exerction of venom and its toxic products and thereby diminishing kidney damage.

Amputation of the part above the bite has been proved to be effective if performed *immediately*.

The absorption time of lethal doses of snake venom has been determined

by experiment. Acton and Knowles injected 100 mgm, of cobra venom into the tips of the tails of four dogs and amputated them 7.6 cm, above the site of inoculation at one-minute intervals. All the animals died within a period of 45–85 minutes. Later, Fairley found that, in sheep bitten over the metacarpal bones by tiger snakes, ligature and excision saved life only when applied within two minutes.

The next steps must be directed towards destroying the poisons remaining at the site of injection. This is best effected by freely incising the bite in the direction of the lymphatic and venous circulation. The wound should be well swabbed out with a strong solution of potassium permanganate; this destroys any toxin with which it comes in contact. Some advocate rubbing in permanganate crystals. Acton and Knowles advocated injection of 10–20 ml. of a 5 per cent, solution of gold chloride in ox-bile as an improvement on permanganate, and at a later date stated that dichloride of platinum (1 in 2000) is even better. Unfortunately, both these substances cause necrosis of the tissues.

A method of treatment strongly advocated by some workers consists of cruciate incision at the point of the bite, and a ring (or more than one ring) of similar incisions ½ inch deep, at the advancing edge of the swelling. These are made in order to induce hamorrhage, when some form of suction is applied in an attempt to withdraw the venom from the tissues. Injection of several hundred ml. of 1 per cent. salt solution into the incisions may help, if followed by suction for ½ 1 hour, repeated for 20 minutes each hour for 10-15 hours. A special suction cup is useful.

Alcohol and strychnine were formerly regarded as antidotes, but are now known to be quite inefficacious.

Carbolic or Lifebuoy soap as first-aid treatment is a practical method advocated by Ahuga and Brooks (1946). It has long been known that soaps can detoxicate snake venom. Carmichael, Cesari and Boquet showed that ricinoleate was anti-toxic in vitro. Success is obtained with Lifebuoy soap in 5 per cent, solution infiltrated at the site of inoculation and appears to be effective, after the lapse of 1½ hours, and even longer, if followed by antivenene. If a finger is bitten, a tourniquet is applied at the base and another above the elbow, similarly with the toe. Then 5 per cent, soap emulsion in a sterile syringe should be injected, 0.5–1.0 ml., at points surrounding the bite; 5 ml. in all should be given and bleeding encouraged by crucial incisions with a razor-blade.

Serum treatment.—It has long been known that immunity could be produced in animals by repeated and progressive inoculation of venom; and a similar result is produced in those who have been repeatedly bitten by snakes. This immunity, however, is specific only for the venom of that particular species. Calmette attempted to produce, in antivenene, a serum active against all snake venoms, but his plain has not been substantiated.

The serum propared against cobra venom is found to be anti-toxic to the homologous venom, and to a certain extent to that of Bungarus fasciatus, but is without action on the viperine venoms of daboia, Echis, Trimeresurus, and Crotalus. The serum produced against daboia venom has no action whatever upon the venoms of Naja, Bungarus, etc. On the other hand,

it has been shown that the hæmolytic properties of Indian and African cobra venoms are practically identical, and the antivenene prepared in India against Naja naja is equally serviceable against N. flava, and that prepared in South Africa against N. flava acts similarly against the former.

In practice the very important drawback to use of antiserum is that, though specific towards some other species of snakes, it may be impotent for the particular species concerned. The practical method of meeting this unfortunate circumstance is to issue an antiserum effective against the most common and the most dangerous snakes in any given district.

All autiveneues are relatively weak in their action as compared to antidiphtheritic and antitetanic sera. The antivenene should be injected intravenously in large amounts as soon after the bite as possible. Acton and Knowles demonstrated that such a serum must be given before the minimum lethal dose of venom has been absorbed, and that it requires some ten minutes to find its way into the circulation. The injection should be made intravenously, and at least 100 ml. should be given. In India serum treatment, if available, should be employed in every case, on the chance that the snake concerned was either cobra or daboia. The longer antivenene is withheld, the greater is the dose required to save life. Early application of the tourniquet, by its localizing influence, reduces the effective dose of serum by one-half to one-third.

There is still much work to be done before an efficient polyvalent serum can be produced. One of the difficulties is that every injection of venom into the horse for the production of immunity gives rise to abscess-formation, and that the whole process lasts from a year to a year and a half. It is estimated that in Brazil the death rate from snake-bite has, by prompt antivenene treatment, been reduced from 25 to 2.5 per cent.

Other measures.—Little else can be done, except to keep the patient warm. Small doses of alcohol, ammonia and strychnine should be given as stimulants, but the practice of exhibiting heroic doses of alcohol cannot be too strongly deprecated. Rogers has advocated, on physiological grounds, adrenalin in those snake-bites in which the toxins have a marked paralytic action upon the vasomotor centres. Acton and Knowles suggested artificial respiration for colubrine poisoning.

VENOMOUS LIZARDS

All lizards are absolutely non-poisonous, with the exception of a single genus, easily recognized, inhabiting Mexico and Arizona. *Heloderma* consists of two species, suspectum and horridum, both heavy, stout lizards, yellow or shrimppink in colour, with black bead-like scales. They are desert-dwellers, and store fut in their swollen tails to tide them over periods of famine. Popularly known as the "Gila1 monsters," they were first discovered near the village of Gila.

The poison apparatus is in the lower jaw, where venom-secreting submaxillary glands are connected by ducts with grooved teeth. Symptoms of poisoning start with paralysis. A large dose produces dyspnæa and convulsions. Postmortem examinations on experimental animals show a greatly dilated heart and venous congestion of the internal organs. Changes in the spinal-cord ganglion cells have also been observed.

Poisonous Fishes

Poisonous fishes exist in most tropical waters, especially among the coral reefs of the Pacific and Indian Oceans. Their venom may be conveyed to man either through the bite or by stings. In one case the poison is secreted by certain epithelial glands within the mouth; in the other, by poison-glands connected with barbs in the dorsal fin. The former comprise more than one hundred species of the genus Murana, all of which possess powerful teeth capable of inflicting bites (Fig. 204). The poison secreted by the glands courses down the hollow teeth. The effect of the venom on man is neuro-cardiac. The latter contains a great number of widely separated genera. In some, the poison finds its way to the exterior only when the barbs are broken, and produces severe inflammation in the wound and, it may be, tetanic symptoms. Synanceia, a spinous genus, is widely distributed throughout the Indian and Pacific Oceans, and is one of the Scorpænidæ (scorpion fish); S. verrucosa is the most toxic. The poison apparatus is connected with the dorsal fin. Plotosus anguillaris, known as "machoira" in Mauritius, has a similarly wide distribution; while Saccobranchus fossilis, in the waters of India and Ceylon, produces much the same symptoms.

Over forty species of Scorpana are found in tropical waters. Their integument



Fig. 204. - Murana moronga. (After Culmette.)

is provided with numerous rays, the stings of which may excite convulsions and even cause death. The symptoms usually evoked are pain extending up the limbs, profuse sweating, pallor, dyspnea and tachycardia. There is often also a morbilliform or scarlatiniform rash. Symptoms are controlled by local injection of 5 per cent. potassium permanganate and pain can be mitigated by infiltration of 2 per cent. procaine and 1 in 1000 solution of adrenalin.

In South American waters, several species of *Thatassophryne* have dorsal spines containing a central poison-duct connecting with glands. Species of *Trachinus*, in northern waters as well as in the Mediterranean, have two sets of poison barbs situated on the operculum as well as on the dorsal fin. The venom has a general action on the heart, besides a purely local effect.

Poisonous Shelleish

In the South Pacific Islands fatal cases of poisoning may be due to bites of certain shellish of the genus Conus, all of which are adorned with brightly-coloured shells. Six at least are known: Conus tulipa, C. marmoreus, C. striatus, C. geographus, C. textilis, and C. aulicus. They are provided with a long tubular proboseis which can be protruded beyond the shell, and opening into it is a sac containing two rows of hollow teeth. According to Clench and Kondo (1943), the poison is not delivered directly from the poison gland, but probably on to the wounded surface. The symptoms are acute pain, swelling, numbness, and spreading paralysis. There may be early drowsiness, deepening into come and death. When bitten in this manner, the Polynosians make small incisions round the bite to cause blood to flow freely. Fatalities have been reported in North

Australia and Polynesia. The first accident producing serious symptoms was reported by Hermitte (1946) from the Seychelles.

Poisonous Corals and Sea-Anemones

Coral dermatitis results from cuts in the skin which cause indolent lesions from contact with the authozoa. The surrounding skin becomes red, ædematous and itchy.

Sea-anemones of the genus *Hellenopolypus* and *Aktinion* give rise by contact to sponge-fishers' or "Skevos-Zervos" disease, itching and vesication, pustulation, nausea and vomiting being produced. The toxin acts like cantharides, and the lesions are due to urticating cells in the tentacles. Washing with vinegar and the application of olive oil is the best treatment.

Poisonous Sea-Urchins

In the West Indies, especially Barbados, spiny sea-urchins cause septic lesions on hands and feet from punctures by the spines. The two poisonous species are *Tripneustes esculentus* and *Centrechinus antillarum*, which also have poisonous ovaries and eggs. Symptoms resembling fish allergy are produced. This is also sometimes associated with the Mediterranean species.

JELLY-FISH POISONING

Meduse of the genus Obelia contain in their ectoderm numerous clear ovoid bodies, the stinging capsules or nenutocysts, which serve as weapons of offence. The whole apparatus is developed in an interstitial cell (enidoblast) which, as it approaches maturity, migrates towards the surface and at one point is clongated by a delicate process—the enidocil or trigger hair. When this is touched the enidoblast undergoes a sudden contraction and causes an eversion of the thread, at the base of which are minute barbs, which are poisonous and produce a numbing effect. The stings produce a painful local swelling and a disagreeable urticaria, and, in susceptible individuals, shock and collapse.

The Portuguese man-of-war (Physalia) is provided with a characteristic stinging apparatus. From the underside of the float there hang filamentous tentacles (gastrozooids, dactylozooids and branching blastostyles), some of which are long and retractile and contain batteries of stinging capsules which produce severe dermatitis and irritation in the skin of those who come into contact with them.

POISONING FROM INCESTION OF POISONOUS FISHES

Cases of fish-poisoning arising from eating the flesh of fishes containing some intrinsic toxin occur more commonly in the tropics than in more temperate countries. In many instances these fish may be eaten with safety, except at certain seasons of the year; in others the poisonous qualities are acquired only after feeding or living in certain localities.

The barracouta (Sphyrana barracuda), a pike-like fish, is eaten widely throughout the South Atlantic; it is the large examples, especially those that are spawning, which are apt to be poisonous, and the symptoms are mainly gastro-intestinal, with paræsthesia. Natives regard as poisonous fishes which show a whitish, watery fluid when cut up, or a black, purplish discoloration at the base of the teeth.

In these waters Ciguatera poisoning results from eating Sphyrana picuda; within a few hours of ingestion, abdominal pain, diarrhoa and vomiting ensue.

There are various sprats (Clupidæ) in tropical waters which acquire poisonous properties; among them is C. longiceps, a sardine found in Ceylon waters, which occasionally may produce collapse and even death.

Many species of the widespread genus Tetrodon are poisonous, such as the "death-fish" of Hawaii -T. hispidus while other species occur in Japanese and Korean waters. The poison is contained in ovaries and eggs, and causes gastrointestinal and nervous symptoms, sometimes culminating in syncope or coma.

The flesh of certain large fishes normally constituting excellent food, such as the king-fish (Scomberomorus cavalla), may occasionally exhibit toxic properties.

In all forms of fish-poisoning the most effective treatment is to evacuate the poison by washing out the stomach and administering purgatives. Other symptoms must be treated on general lines with stimulants, hot-water bottles. and injections of morphia, if necessary, to alleviate pain.

Scorpions and Spiders (Arachnida)

Scorpions are very common in the tropics, and their stings are very painful and cause a considerable amount of inconvenience, though they are not exactly dangerous, except to young children, in whom, in addition to local symptoms. muscular cramps, profuse perspiration, pyrexia, vomiting and convulsions may be produced. Deaths have been reported from North and South Africa, the West Indies, Mexico, Korea and Manchuria. In Trinidad, glycosuria, hyperglycamia, pancreatitis, and even pancreatic cysts, are described as sequela to scorpion stings.

In Southern Europe and North Africa black scorpions, Euscorpius italicus and Buthus maurus, in Mexico the "durango" (Centrurus), in Brazil Tituus servulatus, in Manchuria Buthus martensi, are dreaded (Fig. 205). In South Africa the genera are Hodogenes, Opisthophthalmus and Parabuthus.

Paired poison-glands are situated in the last or postanal segment of the tail which is jointed and very flexible, so that it can be curved forwards over the body when the scorpion is striking. The venom which it ejects is in many respects like that of the cobra, but far less toxic.

Fig. 205 .- Scorpion (Buthus sp.). Half nat.

Mohammed (1943) isolated the toxins in amorphous and crystalline form by grinding up dried poison glands with quartz sand. extracting with normal saline, clarifying by aluminium sulphate and precipitating by acctone. The refined toxin is so active that 0.01 mgm, will kill an albino rat.

> In South Africa Grasset and colleagues have found neuromotor symptoms follow intravenous injections of the three main genera. Neurotoxins and hamorrhagins have been isolated from the genus Parabuthus.

> In the treatment of seorpion-sting in children, it may be necessary to incise and thoroughly wash out the sting with a strong solution of potassium permanganate. In adults, pain is the predominating symptom, and this, according to Tomb, can be immediately relieved by a drop of liquor ammoniae fortis, applied with the stopper of a

bottle. A more liberal application of diluted ammonia is also effective, but not so immediate in action. Dyce Sharp, from experiences mostly in his own person, advocated immediate injection of an ampoule of novocain and adrenalin in the vicinity of the sting. For the severe intoxications of children, Todd produced an efficient antitoxin. The venom extracted from dried stings and venom-glands by normal saline is toxic to horse, goat, and most laboratory animals; while the desert fauna, such as desert rat, jerbon, fennee fox and hedgehog, are immune. The antitoxin has been prepared from horses by subcutaneous

injection of graduated doses of venom. In doses of 5 ml. it exerts both prophylactic and curative action. Sergent states that severe symptoms disappear very rapidly after serum injection.

Spiders. - Nearly all spiders (Aranew) possess poison-glands, the venom of which is injurious to insects, but few are dangerous to man. Certain of the genus Latrodectus are poisonous. In New Zealand one, L. hasselti, is known as the "katipo," Maori term for "night-stinger." In Southern Europe, L. tredecimquitatus, the "malmignatte" (Fig. 206); in Palestine and North Africa, L. lugubris and L. revivensis, in North and South America, L. mactans, L. curacaviensis, and L. geometricus are credited with toxic properties.

L. mactans is known in California as the "Black widow spider"; the adult female is glossy black with crimson hourglass markings on the abdomen; in Turkestan L. tridecimguttatus is the "Karakurt spider"; in Australia, Atrax robustus is "Funnelweb spider" and in South Africa L. indistinctus is known as "Kroppie spider."

The toxin of the poison-glands has been shown to be a powerful hamolysin, causing inflammation and cedema at the site of injection, together with numb-

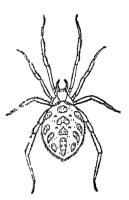


Fig. 206 .- Widow Spider (Latrodectus 13-guttatus. × 2). (After Hirst, "Journ. Economic Biol."

ness of the part and, it may be, urticarial rash. Most observers describe intense nerve-pain, which is said to be due to stimulation of the myo-neural junctions by the venom. Rigidity and spasm of most of the muscles supervene, especially those of the abdomen, which becomes "board-like," simulating appendicitis. Sloughing of the skin in the neighbourhood of the bite may occur.

Treatment consists in washing out the wound with a solution of potassium permanganate (1 in 4000), and administering it by mouth in doses of one teaspoonful every two hours.

Intravenous injections of calcium gluconate (10 ml. of a 10 per cent. solution) are said to relieve the pain and decrease the muscular spasm. In South Africa a serum which neutralizes the venom of L. indistinctus has been prepared by Finlayson, and similar methods have been used in the Argentine and Russia against local species of Latrodectus.

In Peru a pruning spider, Glyptocranium gasteracanthoides, which lives in the

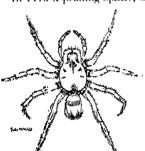


Fig. 207 .-- Tarantula Spider (Lycosa tarentula). Half nat. size.

leaves of vines, and is identified by its ash-grey colour and large globular abdomen with two prominent tubercles, produces, according to Escomel, the same symptoms as Latrodectus, and sometimes hæmaturia.

The "tarantula" spider, Lycosa tarentula 207), occurs in Southern Europe. Mysterious properties have been attributed to its bite; apparently in some specially susceptible people ædema of the cyclids and pyrexia are apt to result, and gave rise to hysterical manifestations known in the Middle Ages as "tarantism." The tarantulas of tropical countries are bird-eating spiders of the family Mygalidæ. They are trap-door spiders, terrestrial in their habits, with prominent projecting mandibles which give them a terrifying appearance. The North African species, *Chatopelma olivacca*, is feared by Arabs, and its bite is said to give rise to acute inflammation.

CENTIPEDES (MYRIAPODA)

The Chilopoda, to which the poisonous genus Scolopendra belongs, are widely distributed in the tropics. They are large creatures, and possess a poison apparatus at the base of the first pair of appendages, which are modified to form jaws. The tropical species, Scolopendra morsitans, reaches a large size, up to 6 in.; the venom causes both local and general symptoms. The site of the bite becomes inflamed and the starting-point of lymphangitis; dizziness, headache, and vomiting may ensue.

Treatment consists in bathing the part with a strong solution of ammonia, I in 5 or 1 in 10. It may be necessary to give hypodermic injections of morphia to

allay pain.

TICK PARALYSIS

Paralysis from bites of *Lxodes pilosus* has long been recognized by sheep-farmers in South Africa. The disease can be reproduced in sheep and guinea-pigs and it has been proved that the virus can be reproduced by the gravid female tick.

Hadwen first found that the tick, Dermacentor andersoni, in the dry districts of British Columbia, gave rise in man to a peculiar paralysis which may prove fatal. This has been reported from North-West States of America and Canada, from the coast of East and West Australia, Cape Colony, Crete, France and Jugoslavia. In America D. variabilis is also responsible; in Australia it is Ixodes holocyclus and I. ricinus; in South Africa I. pilosus, Huemaphysalis cinnabarina and Rhipicephalus simus (Zumpt). A few days after the attachment of the tick the patient complains of weakness of the legs, then an ascending flaceid paralysis develops, affecting both arms and legs, sometimes with loss of sphineter control. Reflexes are diminished or absent and there may be restlessness and aching of limbs, vertigo, photophobia and vomiting. Signs of bulbar involvement such as respiratory distress, dysphagia and dysarthria may develop suddenly. Death is due to respiratory paralysis. Otherwise the patient recovers completely in 48 hours.

To prevent the onset of paralysis, removal of the tick must be complete, as Clunies Ross and others have shown that the salivary glands are sources of the toxin. A protective serum has been introduced for the treatment of tick paralysis in dogs and has been used successfully in several human cases (Gordon, 1946).

CHAPTER L

MYIASIS AND LEECH INFECTION

Under the term "myiasis" it is eastomary to include a number of traumatic conditions of the tissues caused by partial parasitism by the larvæ of certain muscoid flies.

Some of these flies deposit their eggs or larvæ in wounds or in the natural openings of the body; in other cases the grubs, on hatching, burrow into the subcutaneous tissues: others imitate the habits of a tick, and emerge from their hiding-places to feed on blood by puncturing the skin. Intestinal myiasis appears to be an accidental condition in which the larvæ pass through the intestinal canal.

NASAL, AURAL, AND OCULAR MYTASIS

The serew-worm fly, Cochliomyia hominivorax (Appendix, p. 1058), is common in America, ranging from Canada to Patagonia. Most active during the heat of the day, normally depositing its eggs upon open wounds or on dead animals, it attacks people sleeping in the open air, especially those who have any offensive discharges.

Comparatively often the fly lays its eggs in the nasal and aural cavities, as well as on open sores. The larvæ, known as screw-worms, burrow into the tissues, devouring in their passage mucous membrane, muscle, cartilage, periosteum, and even bone. They may penetrate the brain and cause death. Callitroga (Cochlomyia) americana is attracted to wounds and sores. Epidemics of myiasis due to this fly have been reported in Chile by Tobar and Honorato.

Chrysomyia bezziana (Appendix, p. 1058), is a true myiasis-producing fly never breeding in dead but always in living tissues. It has a wide distribution, being found in India and Cochin-China. It appears to have a predilection for human beings in India, the female, as in C. hominivorax, laying her numerous eggs in the masal cavity or in tissues from which offensive discharges emanate. In the S. Pacific in the 1939-1945 war Chrysomyia megacephala and Phormia regina (a greenbottle) were responsible for traumatic myiasis. A douche composed of 15 per cent. chloroform in light vegetable oil was successful.

Rhinostrus purpureus (Æstridæ).—The larvæ of this species are parasitic in the nasal passages of equines in Southern Europe, Asia Minor and Africa, but occasionally the fly attacks man, depositing its eggs in or near the eye, where the larvæ may be seen, moving beneath the conjunctiva, where the destruction they cause may lead to blindness. (See Appendix, p. 1063.)

Wolfahria magnifica (Appendix, p. 1058) of the family Sarcophagida, or flesh flies, is the only specific myiasis-producing fly found in man in Europe, but has a wide distribution in Asia Minor and Egypt. In habits it is similar to the species described above. W. vigil (Walker) is found in E. and N. America.

Ocular myiasis (ophthalmomyiasis).—In tropical and subtropical countries the larve of flies may be deposited on the lids and in the conjunctival sac, whence they may pass into the lacrymal passage, penetrate the conjunctiva and sometimes the selera, and so gain entrance to the intra-ocular tissues. The species are Rhinastrus bovis, Hypoderma bovis, H. lineata, Gastrophilus intestinalis and G. equi. MeBride recorded conjunctivitis due to larvæ of the bot-fly (Estrus ovis) in the conjunctival sac.

SUBCUTANEOUS MYIASIS

In South America the "macaw-worm" or "Ver macaque" (p. 1063) (Dermatobia cyaniventris) infests cattle, indigenous mammals, and also man.

The eggs are deposited on the skin of human beings, and do not hatch for a day or two. Then the larvæ penetrate the skin, producing an inflammatory tumour, from the aperture of which exudes scropurulent fluid containing black fæces. These have been recorded from various regions of the body, and their presence is usually accompanied by great pain. Busek reported that before they reach maturity the larvæ moult and protrude from the apertures in the skin. In removing them there is no need to use a knife, for the exit aperture may be widened by stretching with forceps; the larvæ then slips out, aided by properly applied pressure.

In tropical Africa, the tumbu fly, or ver du cayor (Cordylobia anthropophaga, p. 1058), produces the same lesions. According to Roubaud, Blacklock, and Thompson, the eggs are first deposited on the ground, and the active young maggot attacks and penetrates the skin of its host, especially on the forearm, scrotum, upper part of the thigh and buttock. The lesion resembles an inflamed

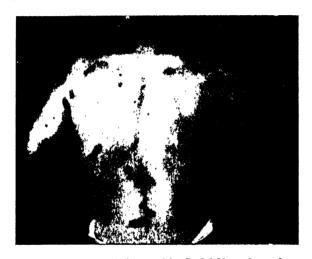


Fig. 208.—Lesions on back caused by Cordylobia anthropophaga.

tumour, from which the larva emerges in six or seven days. These tumours do not usually suppurate (Fig. 208). The fly attacks other mammals besides man. Cutaneous myiasis with fistulous tracts of the mentum has been described in Panama (1948) by Calero due to Stephanostoma hamorrhoidalis (Fall).

LARVA MIGRANS

Synonyms.—Mylasis Linearis; Creeping Eruption; Dermatitis Linearis Migrans.

This condition (Fig. 209), first described by Lee in 1874, and at a later period by Crocker, is said to be common in Russia and, according to Kirby-Smith, extremely frequent in Florida. Certainly it is not infrequent in the tropics, especially in Ceylon and South Africa. Here multiple lesions on the legs and feet are produced by a larval nematode burrowing under the skin; this was shown by Kirby-Smith to be that of Ancylostoma braziliense, a common parasite of cats and dogs. These observations were confirmed by Fülleborn, who demonstrated that similar lesions may be artificially produced in volunteers by the

larvæ of Ancylostoma stenocephala, and, to some extent also, by A. caninum. Shelmire, Heydon, and Fülleborn in self-inflicted experiments showed that ædema and irritation are considerable. The larvæ of Gnathostoma spinigerum have also been incriminated.

Children are mostly attacked between the fingers and toes.

Unlike the itch-mite, the ancylostome larva burrows on indefinitely, like a mole, and forms a red line or narrow raised ridge $\frac{1}{6}$ in. broad. The parasite appears to travel at the rate of $\frac{1}{2}-1$ in. in twenty-four hours. The line zig-zags and twists about, but does not bifurcate, and may be found in any part of the body—the face, chest, or more particularly the soles of the feet and the legs. While the advancing end of the line progresses, the opposite end fades away (Fig. 210). The disease may be of very long duration, and is accompanied by intense itching; sometimes bulle are formed (Fig. 211).



Fig. 209.—Larva migrans. Infected at Durban, April 20, 1921; first symptoms noted July 22, 1921.

In South Africa, especially in Natal and Zululand, where "creeping cruption" or "sand-worm," as it is called, is very common, Murray (1939), by aid of cedarwood oil technique, proved that sometimes the burrows are produced by a mite, possibly related to Tetranychus molestissimus, which is found in Argentine and Uruguay, attacking man and animals. The tracks in the skin are 0.33 mm. in diameter. The mite, and its eggs, are easily demonstrated at the end of the burrow. A drop of distilled water on a clean slide prepared with Mayer's egg albumin facilitates this procedure.

It is possible, as Fülleborn and da Rocha-Lima suggested, that the tropical form differs from that described in Russia and America. The former appears to be due to the burrowing under the epidermis of fly larvæ which have been identified as those of Hypoderma, Gastrophilus hæmorrhoidalis, and G. veterinus. The lesions of the ancylostome larvæ group can be distinguished from those of Chastrophilus by being shorter and more complex.

Austmann used Lombard's method of clearing living skin to demonstrate larvæ of Gastrophilus in cases produced by this insect. Ordinary machine-oil is used and the epidermis cleared around the line of creep. Using the binocular

dissecting microscope, the parasite may be seen lying between the cornified and granular layers of the epidermis. With a magnification of 150 diameters, details of structure can be clearly seen.

In Florida creeping cruption has a definite seasonal prevalence during the summer months, after periods of rainy weather. Most cases originate on the beach above high water mark. There is some evidence that it is connected with sewage disposal. Dogs and cats are the hosts of the adult 1. braziliense.

Treatment.—Excision of the portion of the burrow containing the advancing larva may be attempted, though refrigeration with ethyl chloride has been found effective. An area of one and a half inches at the visible end of the burrow should be frozen for two to four minutes. The spray should be directed about half to one inch in front of the inflamed end of the burrow. If the burrows are multiple, it should only be applied to a few at a time.



Fig. 210.-Multiple burrows of larva migrans, from the Gold Coast.

Bayley (1941) claimed that the most scientific treatment consists of locating the larva by means of the ecdarwood oil method, then injecting 1 in 1000 procains in order to desensitize an area of over half an inch in diameter with the larva in the centre. A cautery is then applied until a small burn is produced. Sulphonamide, 0.5 grm. for two days, helps to heal and prevents secondary infection. Each burrow must be examined in turn. According to Kelsey, refractory cases are best treated by diathermy, using the needle point of the apparatus with a 16 in. spark. Intradermal injection of 30 per cent. N/methylglucamine antimonial (Glucantine) 1 ml. into each site affected at the end of the canal every fourth day is recommended by Gambini. Loewenthal (1950) in the treatment in S. Africa recommends hetrazan in doses of 2 mgm. per kg. thrice daily and this has been found to be particularly successful. The natural duration of this disease is about four months. By this method it is reduced from 13-28 days. Improvement was rapid in 2-17 days. Control measures consist of excluding dogs and cats from the beaches, restricting bathers to that part washed by the tide, wearing shoes, and treating dogs and cats with tetrachlorethylene to remove adult worms.

BLOODSUCKING LARVE

Auchmeromyia lutcola (Appendix, p. 1060), the larva of which is commonly known throughout the Congo as the "floor maggot," has a wide distribution throughout tropical Africa, from Northern Nigeria to Natal. The adult fly is usually found among the thatch and beams of the walls and roofs of native huts, and deposits its eggs in erevices of the mud floors. Here the larvæ hatch and move about in the moist earth. They emerge from their hiding-places to feed mainly at night.

Sucking of blood is effected in a curious manner: the head segment is retracted, and the lips of the second form a sucking disc attaching the larva to the skin of its host; the skin is scarified by curved hooks, and thus blood is drawn. The larva soon assumes a red colour due to absorbed blood. It is said that the bite is non-irritating.

INTESTINAL AND URINARY MYIASIS

Residence in the alimentary canal of some vertebrate animal is a regular feature in the life-history of many dipterous insects. The eggs are either licked from the skin or swallowed in the food on which they have been deposited. In this way they are transferred to the stomach, where, after an interval, the larvæare hatched out and undergo development. In due course they appear in the fæces. Man is not infrequently victimized, especially in tropical countries. Sometimes, until a correct diagnosis is arrived at, not a little alarm is caused by the appearance of these creatures in the stools or vomit. They are easily recognized. The ringed, cylindrical body, ½-1 in. in length, according to species, broad at one end, tapering at the other, and usually beset with little spines or hairs, is sufficiently diagnostic (Fig. 211).

Already over twenty species of diptera are recognized whose larvæ have been found in or expelled from the intestinal canal. The commonest form is C, romitoria.



Fig. 211.—Larva of Calliphora vomitoria.

In Europe the majority of cases of intestinal myiasis, a not infrequent occurrence, are caused by Fannia canicularis and F. scalaris (flies closely resembling the common houselly, and erroneously considered a young form of the latter on account of its smaller size). Occasionally, pains in the abdomen, vomiting, and diarrhoan may ensue, and there may be evidences of toxic absorption; more usually these occur when the ingested larvæ are those of the cheese maggot, Piophila casei. Larvæ of the common housefly (Musca domestica) have been found in numbers in the stomach in the Philippines. In Africa the insect commonly found is Chrysomyia chloropyga, and occasionally C. putoria.

A dose of castor oil will probably suffice to expel any of these creatures that may not have been passed spontaneously.

Rational prophylaxis consists in covering up food after it has been cooked, in order to prevent the access of flies.

Instances in which larvæ of *F. canicularis* and *F. scalaris* have been discharged per urethram have also been met with, though more rarely.

LEECH INFECTION

In the grass and jungle lands of many tropical and subtropical countries land-leeches, probably of special species, often occur in great abundance; so much so that in some circumstances they may prove more than a nuisance. Hæmadipsa zeylanica in Ceylon is one of the most active, as well as best known. Before feeding, when outstretched, it is about an inch in length and about the thickness of a knitting needle. It clings to a leaf or twig, awaiting the passing of some animal, on to which it springs with remarkable activity. It can insinuate itself through the meshes of the finest stockings. It at once attaches itself to the skin and proceeds to make a meal of blood. Animals are sometimes killed: men even have been known to succumb to repeated small bleedings by these It is necessary, therefore, when passing through jungle lands in which leeches abound, to have the feet and legs carefully protected. The bite is not infrequently the starting-point of a troublesome sore. Leeches abound in After rain a traveller in the jungle is likely to find his boots full of Malava. blood.

In the south of Europe and in the north of Africa the horse-leech, Limnatis nilotica (Fig. 212), which lives in ponds and other collections of water, sometimes finds its way into the gullet and nostrils; and has occasionally caused death by entering and occluding the air-passages. These leeches are a source of inconvenience to French troops in Algeria, and are mentioned as troubling Napoleon's army in its retreat through Sinai; several cases have been noted among British troops during the Egyptian and Palestine campaigns in 1914–1918 and again in 1939–1945 wars (Reeves). In Formosa, Manson heard of and saw several instances of a similar form of parasitism, both in men and in monkeys.



Fig. 212. - Limnatis nilotica, Half nat. size. (Sheppard, del.)

Doubtless, when very young the leeches are taken in unperceived with foul drinking-water, and, wandering round the soft palate, find their way into the nose. For a long time they contrive to clude all attempts at capture, but can generally be persuaded to show themselves by dipping the face in cold water. An American naturalist, who had been travelling much in the interior of Formosa, had suffered from severe headache and profound anamia, the results of repeated epistaxis. Manson succeeded in removing a leech by attaching to its hinder end, through a speculum, a spring forceps, and afterwards injecting salt and water. Therefore in tropical countries persistent headache, associated with recurring epistaxis, may be caused by a leech in the nostril. A protective chemical known as 0960 has been found by Andy and Harrison. When garments are impregnated with this, leeches are repelled even after seven cold washings.

In Japan H. japonica is found; in the Philippines H. talagalla; in Java H. javanica. Other species are H. fallax from Madagascar. Others such as H. morsitans and H. vagans constitute a scourge in Sumatra, New Guinea, Celebes, Borneo, French Indo-China, Chile and Trinidad.

Section XI.—SPECIAL SUBJECTS

CHAPTER LI

TECHNIQUE OF INJECTION AND BLOOD TRANSFUSION

INTRAVENOUS THERAPY

Preparation of the patient.—The patient should preferably be placed in a sitting position, with his arm resting on a board or other firm object. The median-basilic or -cephalic vein at the bend of the elbow usually offers the best site for injection, both being easily visible and situated close beneath the skin. The veins are rendered prominent by instructing the patient to clench the hand. The vessels in the upper arm are constricted by a piece of moderate-sized rubber tubing (! in. in diameter), elipped by a Spencer Wells forceps or by the arm-band of a blood-pressure apparatus, so that the pressure can be released subsequently with ease. In certain cases the distended vein can be felt distinctly under the skin with the examining finger, even when it cannot be seen. Fat subjects often present considerable difficulty, and it may be necessary to use distended veins on the dorsum of the hand.

The site having been selected, the skin is sterilized by a strong solution of iodine, which should be removed by ether or strong spirit.

Method of injection.—The syringe is now filled with the selected drug; this is best done by drawing up the solution from a sterile test-tube, or other glass receptacle, care being taken to exclude all air-bubbles.

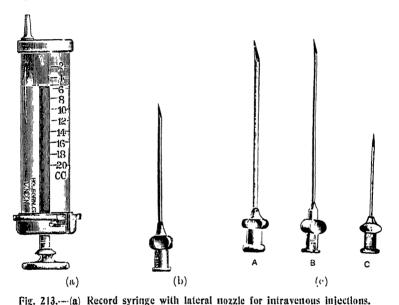
The needle should be plunged into the vein. Penetration should be effected in two stages, first through the skin, and secondly in an upward direction into the lumen of the vein. When the needle is felt to be inside the vein—usually within \(\frac{1}{2} \) in. from the surface of the skin—the plunger should be slightly withdrawn; blood will then well into the barrel. Directly this is seen, the tourniquet should be loosened and the injection steadily made. When it is completed, a finger should be pressed over the site of injection and the needle withdrawn. Great care should be taken not to transfix the vein; in that case the solution is injected into the tissues behind the vessel and may cause inflammatory disturbances, or even absecss.

The syringe and needles.—For most purposes a 10-ml. Record syringe is satisfactory, though for the injection of serum one of a larger capacity, up to 20 ml., may be required. The type fitted with a peripheral nozzle (Fig. 213a) is most suited for intravenous therapy. It is advisable to test the syringe before use by drawing up boiling water, for often the plunger, on becoming overheated, sticks in the barrel.

Success depends to a very great extent on the sharpness of the needle. If possible, a new steel-wire needle should be used on each occasion. The size is also important; a stouter type than that used for subcutaneous injection is necessary; about No. 12 is the most suitable (Fig. 213b).

In view of the danger of conveying virus diseases, especially infective hepatitis, by syringes, it is pointed out that the only processes which ensure absolute safety are autoclaving or exposure to a temperature of 160° C. in a dry oven. The cement of glass-metal syringes may even melt at those temperatures.

Therefore the use of all-glass syringes is advocated and these should be enclosed in tubes, the ends of which are tied up with Kraft paper or cellophane, and they should be sterilized preferably by dry heat. Boiling is an alternative, but it cannot destroy spores, though addition of sodium bicarbonate to the water will remedy this fault, and the resulting alkalinity of the syringe may affect drugs or biological products. There is no suntable chemical method for sterilizing a syringe and the use of alcohol is not recommended, except for insulin or adrenalin. In mass intravenous injections a fresh syringe is advocated for each patient, in order to avoid the risk of transmitting epidemic hepatitis. In Switzerland glass-metal syringes are obtainable marked 200° C, the cement of which does not melt below this temperature. "Tubunic" ampoules are ampoules filled with sterilized drugs in solution, such as quinine, provided with



(b) Intravenous or infrantscular needle, size No. 12.
(c) Various sizes of exploring, scrum, and hypodermic needles.

A, Aspiration needle. B, Interanuscular needle. c, Hypodermic needle, No. 16.

a needle protected by a glass covering, ready for injection, and can be discarded directly after use.

Needles (Fig. 213c) keep best if smeared with vaseline, or kept in carbolized oil. Plunging the needle-points into a block of hard paraffin wax will prevent them from rusting.

The preparation of non-pyrogenic distilled water is effected by using activated charcoal. Pyrogen is a thermostable product of the metabolism of certain strains of bacteria, and their antigenic products may develop in the distillate from ordinary water by contaminating organisms if permitted to stand unsterilized for more than 24 hours. Even when derived from a contaminated source it may contain sufficient pyrogen to give a reaction, even when sterilized immediately. The removal of the pyrogen is effected by shaking up with 0-1 per cent. "depyrogenizing charcoal."

BLOOD TRANSFUSION

Blood groups!.--ABO blood group system is composed of one of four groups:--

$.1gglutinogens\ in$		Agglutinins in			
	red cells	serum			
AB	A and B	Neither			
Λ	A	Beta (anti-B)			
\mathbf{B}	В	Alpha (anti-A)			
()	Neither	Alpha and $Beta$			

Agglutination of red cells takes place whenever homologous agglutinin and agglutinegen come into contact; therefore, homologous agglutininagglutinegen cannot coexist in the same

blood.

There are now eight distinct blood groups in man. By blood group system is meant a system of antigens present in human red cells whose inheritance is determined by genes situated in the same part of one chromosome. The inheritance of the four original blood groups is quite independent of the Rh system. There are also iso-antibodies which do not agglutinate red cells, but which nevertheless give specific reactions when tested for by the indirect antiglobulin method.

The equivalent antibodies determine the clinical importance (1) during transfusion when interaction between antigen and antibody may be associated with rapid blood destruction, or (2) during programey, when the antibodies may cross the placenta from the mother and so damage the fectus.

Only the ABO and Rh systems are commonly involved in hemolytic transfusion reactions and one only, Rh, is commonly involved in hemolytic disease of the newborn.

The other blood group systems are of less importance and practically never cause trouble at the first transfusion, so that, if a person has had a provious blood transfusion, matching must be carried out with special care.

Iso-antibodies are divided into two classes: naturally-occurring and immune.

Naturally-occurring and immune.

Naturally-occurring antibodies agglutinate red cells suspended in saline and act more strongly

at 4° C. than at 87° C. and are then incapable of causing destruction of red cells in vivo.



Fig. 214.—Apparatus for intravenous injection, with regulating clip on tube, and special form of intravenous needle.

^{*} For full information on this intricate subject the reader is referred to:
 "Blood Transfusion in Clinical Medicine" (1951) by P. L. Mollison and "Rh Groups and their Clinical Effects" (1951) Medical Research Conneil Memorandum No. 19.

Naturally-occurring agglutinins, either fail to pass the placenta, or at best do not do so readily.

Immune iso-antibodies are more active at 37° C. than at low tempera-

tures and pass the placenta readily.

The presence of antigens in the red cells is determined by *genes*, although in most cases no distinction need be made between *genes* and *antigens*. If a person inherits a certain gene the corresponding antigen can be detected in his red cells, provided the appropriate antisorum is added.

These genes are carried in chromosomes which are present in pairs and the *genes* controlling one particular system are conceived as lying opposite to one another, so that any effects produced are the action of two sets of genes. The inheritance of the ABO group depends upon the three genes A, B and O. The relevant chromosomes in the sex cells carry only one of

these genes whilst the body cells contain two.

Thus an individual inherits A, B and O from one parent, and A, B or O from the other. The sum of genes present in the body cells determines the genotype of the one person and thus six genotypes can occur -AA, AB, BB, AO, BO and OO. If A is absent from one person's red cells an anti-A agglutinin is found in the serum, and if B is absent, his serum contains anti-B agglutinins. Various subgroups of A and B are recognized, but, unless the recipient has been sensitized by a previous transfusion, they are not of much practical importance.

In most populations 40-50 per cent, of individuals belong to Group O. During the last few years it has been realized that the anti-A and anti-B agglutinins present in Group O blood involve a definite risk to recipients

who are of other groups.

In determining blood groups, unknown cells are tested with anti-A and anti-B serums containing alpha and beta agglutinius. If agglutination occurs with both, the cells must contain A and B agglutinogens and therefore belong to group AB; but, if agglutination occurs only with alpha or Anti-A serum (from group B donor), then the red cells contain A agglutinogen and belong to group A, but, if it occurs with beta, or anti-B serum (from Group A donor), the cells contain B agglutinogen and belong to group B. If it does not occur with either serum, the red cells contain neither agglutinogen and belong to group O.

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More reliable results are obtained when both serum and cells are tested. The dual test provides a check on possible technical errors. This should, under present conditions, always be made.

Sub-groups.—There appear to be two kinds of A agglutinogen, so that blood of sub-group A_1 , and A_1B and A_2 , and A_2B occur. The importance of recognizing this sub-division lies in the fact that cells of A_2 , and particularly A_2B bloods, react more weakly than those of A_1 and A_1B bloods

with anti-A test sera; indeed they may react so weakly that reactions are not detected at all, unless test sera are used, which are known to give satisfactory reactions with A_2 and A_2B cells. The main practical significance lies in the need of avoiding erroneous classification of bloods of subgroups A_2 and A_2B as O and B respectively, owing to failure to detect the A_2 factor. Approximately four out of five group A and AB bloods belong to subgroups A_1 and A_1B , and the remainder to subgroups A_2 and A_2B .

When transfusions are given to recipients of A and AB it is unnecessary to use blood of the appropriate sub-group, except in rare cases in which the

recipient has been sensitized by a previous transfusion.

The extra agglutinins associated with subgroups are usually present in small amounts, and are more active in the cold than at room temperatures. At a *first* transfusion they are unlikely to give rise to reactions due to incompatibility between the cells of the donor and serum of the recipient, but such a transfusion may stimulate an increase in the titre of circulating extra-agglutinin and, at subsequent transfusions, the risk of incompatibility will be increased; but in practice this appears to be rare.

The ABO group can usually be determined by examining the serum independently of the cells. If the serum agglutinates B, but not A cells, the patient belongs to Group A. This method provides a check on the

antigen content of the cells.

Collecting blood.—If blood to be typed is taken from the donor not more than a few hours before it is to be used it can be obtained by a skin prick and mixed with 3 per cent. sodium citrate in a tube. The cells should then be washed once in saline and a suspension containing approximately two volumes of red cells per hundred volumes of saline should be prepared. For routine use it suffices to gauge the strength of the red cells suspension by naked eye examination. If the blood is to be stored for more than a few hours before use, a venous sample should be obtained and placed in a sterile container, allowed to clot and kept at 4° C. The clot is washed in saline until the supernatant fluid is clear. Then it is broken up with a Pasteur pipette and sufficient red cells liberated to prepare a suitable suspension.

Methods of testing.—The blood should be examined, both for

agglutinogens in the cells and for agglutinins in the serum.

Test for agglutinogens in the cells. (1) The ideal tube method.—Test tubes 2in. by Jin. are placed in 1st, 2nd, 4th and 5th ten-hole rows of a lifty-hole wooden block. High titre anti-A serum is placed in the tubes of the 1st and 4th rows, anti-B serum in the 2nd and 5th rows. Red cells from the blood to be tested are added to the first tubes in the 1st and 2nd rows, cells from another sample to the second tubes in the same rows, and so on. By using forty tubes in the same block, red cells from twenty samples of blood can be tested against anti-A and anti-B sera.

In each tube there is a volume of serum, red cell suspension and, to avoid false agglutination, a volume of saline. A pipette, graduated at 0.04 and 0.08 ml., is filled to the upper mark and delivers 0.08 ml. of serumsaline mixture. Next, the pipette, after rinsing with water and saline, is filled to the 0.8 ml. mark with red cell suspension in 3.0 per cent. sodium

citrate solution. As controls, cells of known groups A, B and O are put up in the same way. The tubes are shaken, capped with cylindrical glass caps and left at room temperature for two hours.

Reading results.—The cell deposit is dispersed, and the content of every tube which does not show undoubted agglutination examined microscopically. The strength of the reactions is graded as completely visible to the naked eye, visual, or microscopic, when big clumps can be detected.

Tests for agglutinius in serum.—The test is set up as above in pairs of tubes, each of which receives 0.04 ml. of serum. To the first are added known A_1 cells and the second known B_1 cells (0.08 ml. of appropriate cell suspensions).

Rapid tube method.—Many serologists now use a centrifugalization technique for agglutination. The modern method is to set up the agglutinations (mixtures of typing sera and cell suspensions) in Durham tubes 13 by 5 mm, in diameter, and after two minutes standing (to allow absorption of the agglutinin by the cells) to centrifuge the tubes for a few minutes at 1,000 to 2,000 revs. per minute. This centrifugalization increases the sensitivity of the reaction, and also increases the speed at which it takes place.

(2) Tile method with diluted blood.—The diluent may be either normal saline or 1 per cent, sodium citrate in normal saline. These should be recently made up, for if contaminated, false agglutinations may take place. Sufficient blood is obtained to make a 3 per cent, suspension of red cells. If there is any delay the tubes should be kept in a refrigerator between 2° and 4° C. A drop (0·05 ml.) of high-titre anti-B serum (from group A blood) is placed in a left-hand space of an opal glass tile and an equal amount of high titre anti-A serum is on an adjacent right-hand space. To each of these is added 0·05 ml. of red cell suspension. The admixture is rocked and left to stand for 10 minutes and then agitated more strongly. Agglutination can easily be seen and the group read off.

For testing unknown serum. - The technique is the same save that 0.1 ml. drops of unknown serum are placed on the tile and to these are added

0.05 ml. of the appropriate known cells.

With undiluted blood the method is much the same. Drops approximating to 0.05 ml. are removed by pipette, or platinum loop, and transferred to drops of 0.1 ml. of unknown serum. The amount of blood added should be sufficient to colour the mixture light pink. The area covered by the mixture should be 1.5-2 cm. in diameter. After the tile has been agitated, macroscopic agglutination (if it is going to occur) will take place within two minutes. Agglutination which may be seen after 10 minutes is false.

(3) Blood grouping with the agglutinometer technique.—Adaptation of Garrow's agglutinometer for blood grouping provides a rapid, simple and reliable method for use in the field and in small laboratories.

A number of leucocyte-counting pipettes, bottles of other, citrate, etc., are arranged ready for use. The apparatus is easily portable and blood grouping can be performed at the patient's side within a period of three minutes.

The blood is sucked up into a lencocyte-counting pipette to mark I, then the solution of sodium citrate is run in to mark II. One or two drops

of this citrated mixture are expelled from the pipette, and a small drop (0.015 ml.) is placed on each of the first two partitions of the agglutinometer glass slab. A drop of group A serum is placed on the adjacent partition and a similar amount of B serum in the vicinity of a drop of citrated blood on the second partition. With the drops so situated that they easily intermingle, the agglutinometer slab is revolved for one minute and then removed for close inspection. Positive agglutination is readily recognized against a white background or by illumination with an electric torch.

As the glass slab is divided into thirty partitions the blood of fifteen donors can be simultaneously classified. In case of doubt, the emulsions on the slab can be scrutinized under the microscope. Whenever possible in an emergency, direct matching of the donors' blood with the recipients' sorum should be performed by the same technique.

The blood is abstracted in a small test tube which is placed in a water bath at 37° C. for 25 minutes. This promotes rapid clotting. It is then centrifuged for 5 minutes and 0.5 ml. of serum withdrawn for cross-matching.

The tile method can also be used. There are more elaborate methods such as the tube method in albumin, and the indirect Coombs' method when antibodies are suspected from a previous transfusion.

Direct matching of the donor's cells against the recipient's serum before transfusion is important, especially when blood of groups other than O are used. It must not be considered as a substitute for blood grouping which should always be undertaken when grouping sera are available. Direct matching should be omitted solely in an acute emergency. When direct matching cannot be performed known group O blood should be given.

The Rh factor.—The red blood cells of 85 per cent. of human subjects, irrespective of their ABO group, contain a further agglutinogen "Rh" (the term is derived from the fact that a similar agglutinogen is found in the red cells of rhesus monkeys). The importance of this lies in the fact that the remaining 15 per cent., whose red cells lack the Rh agglutinogen, are apt to form an antibody (agglutinin) against the agglutinogen. This may occur in an "Rh negative" woman if she becomes pregnant with a fectus whose blood cells are "Rh positive", or it may happen in "Rh negative" persons of either sex when "Rh positive" blood is transfused.

The discovery of the Rh factor in human blood and the realization that human beings can be classified as Rh positive or Rh negative, according as to whether or not their blood corpuscles are agglutinated by an antirhosus serum has led to the solution of erythroblastosis feetalis and the humolytic reactions that sometimes follow blood transfusions, even of compatible ABO groups.

In 1940 Landsteiner and Wiener found a hitherto unrecognized antigen, "Rh," and later Wiener and Peters showed the presence of Rh antibody in the blood of Rh-negative patients who had suffered hemolytic reactions following transfusions with Rh-positive blood. In 1941 Levine proved that the formation of Rh antibody by an Rh-negative woman frequently

resulted in stillbirth or in one of the syndromes grouped together under the term of "erythroblastosis foetalis" and suggested that the formation of antibody was the maternal response to immunization by Rh antigen. derived from the fœtus, inherited from its Rh-positive father. It soon became apparent that Rh tests must be made as a routine before giving blood, if grave dangers are to be avoided. For instance the giving of Rh-positive blood to Rh-negative persons, who have been sensitized by either a pregnancy or a previous blood transfusion, may kill them. giving of Rh-positive blood to an Rh-negative girl or woman may sensitize her to Rh antigen so that an Rh-positive child subsequently born to her may be stillborn or diseased. Even the injection of a small amount of Rh-positive blood may cause lifelong sensitization. This can be avoided by Rh testing so that never an Rh-positive blood is given to an Rh-negative patient. However, in view of the comparative rarity of preventable Rh sensitization, it is clear that urgently required transfusions should not be withheld, simply because facilities of Rh tests are not immediately available.

Direct matching of the donor's and recipient's blood is a very valuable safeguard against fatal transfusion reactions from Rh, as well as from ABO incompatibility, but it does not constitute a safeguard against the possibility that a transfusion may imitate Rh sensitization and thus lead to future hemolytic disease. When Rh tests cannot be performed all females who have not passed child-hearing age should receive Rh-negative blood. The size of the transfusion is not important. Experimentally, the injection of amounts of Rh-positive blood, as small as 0-05 ml., suffices to produce an optimal antibody response and there is some evidence that the spacing of transfusions is important in determining the antibody response. Probably a few transfusions spread over many months are more likely to induce sensitization than the same number of transfusions given rapidly one after another in the course of a week or two, although there is no direct proof of this.

When an Rh-negative man (or woman who has not been sensitized by pregnancy) receives repeated transfusion of Rh-positive blood, the first transfusions are entirely successful, but sooner or later sensitization develops. At first the transfused cells are eliminated unduly rapidly and it may not be clear that the transfusion has been unsuccessful. If more transfusions are given hemoglobinuria and renal failure are likely to ensue.

The most important Rh antigen is known as D. Every individual inherits the gene D, or its allele, d, from each of his parents. Other Rh genes are C or c and E or e.

Frequency of Rh positive groups.—In N. and C. Europe and parts of S. Europe, as well as in relatively unmixed European populations, the frequency of Rh negative individuals shows an almost constant level of about 16 per cent. The only populations known to have a higher frequency are the Basques, with about 30 per cent. Rh negatives. In many Moditerranean populations a Rh-negative frequency of 5-8 per cent. is found, and about 10 per cent. in Iraq and N. India. In S. India and E. Asia generally,

frequencies vary from 2 per cent. to zero. About 5 per cent. of Negroes are Rh-negative. The aborigines of Australia and the Pacific Islands and of N. America are almost exclusively Rh-positive, except when there has been interbreeding with Europeans and Negroes. Where the frequency of Rh negative individuals lies between 4–10 per cent., as it does in most of the Mediterranean area, in Africa and W. Asia, it is clear that in any blood transfusion account must be taken of the Rh factor, and it must be so arranged that Rh-negative women should be transfused only with Rh-negative blood. It is desirable that Rh-negative men as well should receive nothing but Rh-negative blood (Mourant).

The variants of the Rh factor such as D^u must always be taken into account. This occurs in the chromosome combination CD^ue and CD^uE. All blood for transfusion should be tested with anti-C and anti-E in addition to anti-D and only, if negative to all these three sera, can blood be issued as Rh-negative. Amongst Negroes the incidence of D^u is higher than in Europe and occurs only in this form. Twenty per cent. or more of blood from Negroes which appear to be cde/cde contain in fact D^u antigen and, since this D^u factor has been known to cause hemolytic disease of the newborn in the children of D^u negative mothers, it is important that all bloods should be checked by a test to reveal the D^u factor.

INTRAVENOUS BLOOD TRANSFUSION

Abstracting blood from the donor.—Full sterile precautions should be observed. The upper arm should be constricted with a tourniquet or arm band of a blood-pressure apparatus so that the veins are obstructed, but the radial pulse unaffected. An intradermal wheal of 1 per cent. novocain may be made over the selected vein. The needle is passed through the wheal into the vein and the blood will instantly pour out. It is now steadied in position with the left hand whilst the flask (or bottle), held in the right hand, is lowered below the level of the donor's arm and the contents continuously mixed with a slow rotary movement so that the blood is thoroughly mixed with the citrate, until it is filled to the upper mark. To promote a free flow of blood the donor should clasp and unclasp the hand.

When the flask is filled to the required 330 ml. mark, the second flask is substituted and filled in a similar manner. The tourniquet is released, the needle is withdrawn and a dressing applied. (When it is proposed to store only for 2–3 days there is no advantage in adding glucose to the mixture, but if for longer periods, 20 ml. of 15 per cent. glucose are necessary.) The donor should rest for one hour after being bled and should not be permitted to do any work for the rest of the day.

The anti-coagulant should consist of 100 ml. of 3.8 per cent. citrate in distilled water to which is added 20 ml. of a 15 per cent. glucose in distilled water which must be filtered and autoclaved immediately after distillation. As glucose is apt to caramelize during autoclaving in the presence of citrate, it is necessary to sterilize them separately; 120 ml. of solution is used for 420 ml. of blood.

Apparatus. — Two beakers, or Florence flasks, either graduated or marked at the level of 330 ml., are required, each containing about 500 ml. Needles of short level with uniform bores, but of different sizes, should be

provided, a tube and glass funnel with suitable rubber connections and a needle for giving blood to the recipient (Fig. 215). A glass window should be provided near the needle, so that a view of the contents of the tube can be obtained. The armlet of a blood-pressure apparatus is the best form of tourniquet.

The apparatus is tested and sterilized immediately before use, and 80 ml, of sterile 3.8 per cent, citrate solution are placed in each flask.

Each flask now contains 80 ml, of citrate solution mixed with 250 ml, of blood and there should be no elotting. These proportions allow an ample margin of citration, so that if it is desired to give more than 500 ml, of blood, another 100 ml, can be safely run into each flask. Experience has proved, however, that 500 ml, is a fair average transfusion. The use of two flasks minimizes the risk of losing all the blood through clotting or other accident. If the transfusion is being completed

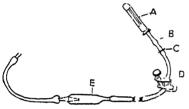


Fig. 215.--Blood transfusion outfit with drip feed bulb.

- A. Stainless steel needle in small test tube.
 B. Record fitting attached to short piece of rubber tubing.
- Male metal adaptor.
- D. Regulating clip. B. Drip feed bulb.

basins of hot water during filling and for some time after, in order to keep their contents at about 104° F., at which temperature the blood will not be injured, and in order to counterbalance the heat lost during the passage through the funnel and rubber tubing.

at once, the flasks should be kept in

For storage. The flasks should be placed at once in a refrigerator and maintained between 2 and 6° C. Blood must never be allowed to freeze. Under these conditions blood may be stored from 10–14 days.

Technique of transfusion. Simple methods of transfusion are recommended for use in the field, and complicated apparatus is too cumbersome for practical use in the tropics. Similarly, methods for transfusing fresh blood direct are too uncertain.

The armlet is applied to the recipient's arm after the skin has been prepared. Hot sterile saline is run through the funnel and tube, and a small quantity of the citrated blood poured in. Air-bubbles should be expelled and the needle inserted into the recipient's vein, the armlet loosened and the blood allowed to flow slowly. When the recipient's voin is not apparent, and there is doubt if it has been entered properly, the shaft of the needle, attached to a small hypodermic syringe, should be inserted into the vein first and the flow of blood observed before connecting At least twenty minutes should be occupied in running in the proper amount, care being exercised throughout to keep the blood at the correct temperature. The collapsed and contracted condition of the recipient's veins often causes difficulties. By making the armlet tight enough completely to arrest the circulation for about ten minutes, the collected carbon dioxide will cause a local vasomotor relaxation so that, if the pressure of the armlet be now reduced to the level of that of the diastolic pressure of the recipient, maximum dilatation of the veins will occur. It is for this purpose that a bloodpressure apparatus is preferable to a tourniquet, though with attention to the pulse the latter can be made to serve. Upon the degree of care with which the recipient's veins are dilated and rendered tense the success of the transfusion often depends.

Evidence of danger.—Evidence that the injection is unsuitable is given by the following signs: lumbar pain, fullness in the head, "pins and needles," præcordial oppression, evanosis, laboured respirations or slow pulse. Any such signs enjoin cessation of the injection at least for a short period. Later, evidence of incompatibility may be shown by rigors, urticarial cruptions, or hæmoglobinuria.

(Bottles for taking, storing and giving blood can be adapted from modified pint milk bottles with an aluminium cap lined with 4 mm. rubber diaphragm and provided with a metal band and loop at the base for hanging the bottle in an inverted position when required to administer blood by gravity.)

Drip transfusion.—Drip transfusion has many advantages over the open method. It is continuous, less likely to provoke reactions and more suitable for patients with profound shock. The patient's arm should be bandaged to a back splint. The bottle containing blood is attached to a stand 3½ ft. above the patient's head. A simple type of drip feed bulb is illustrated in Fig. 214. When this is used, a screw clip is placed below the drip bulb near the needle in order to obtain satisfactory control. The desired flow of blood is about 40 drops per minute. Most drip blood flasks are provided at the affluent with gas mantle filter or gauze plug to remove any possible blood clot. On no account must the flow be allowed to stop, or clot will form in vein or cannula. For prolonged transfusions the Marriott-Kekwick apparatus is employed, in which the blood is constantly stirred by a stream of oxygen bubbles.

Reactions to blood transfusion can be summarized briefly as fever, rigors, pain in the loins, headaches, vomiting and urticarial reactions.

Finally hamoglobinuria constitutes one of the serious manifestations of incompatible blood transfusion.

Reconstitution and administration of dried serum or plasma.—Dried serum is stable and is specially valuable for tropical conditions. The serum separated from clotted blood is filtered and dried in a frozen state. It differs from plasma in the abstraction of fibrinogen. It has the advantage of being tolerated in concentrated form, is beneficial in all forms of shock, and can be given to recipients of any group. It should be kept as cool as possible and in the dark.

Reconstitution.—Dried serum is dispensed in standard 540 ml. bottles containing the solids of 400 ml. of serum. It is reconstituted by the addition of 200 ml. (twice normal concentration) or 400 ml. of specially sterilized distilled water. Solution occurs in twice normal concentration in 20 minutes; in normal in half that time. Solution is accelerated by placing the bottle in a bowl of warm water (104° F.). Solutions of 14 per cent. and 7 per cent. of protein are then available. Reconstituted serum is used as an alternative to blood or liquid plasma. Experience has shown that 400 ml. is a suitable dose.

Dried citrate plasma is similar to dried serum. The plasma is separated from blood which is mixed with citrate diluent. It is bacteriologically filtered and dried from the frozen state, whilst the method of reconstitution and administration is similar to that described for dried serum. The protein concentration is about 5 per cent.

Administration.—Reconstituted serum can be administered by gravity by means of the ordinary funnel apparatus (Fig. 215). A little normal saline should be run in before the reconstituted serum and at least 10-15 minutes should be allowed for each bottle. Finally, a few millilitres of normal saline should be run in to wash the serum out of the tubing.

Transfusion with concentrated suspension of red cells.—This method is now employed in very severe anamic states, especially in acholuric jaundice and other icteric conditions in which reactions are likely to ensue. Less than half the usual volume will produce the same rise in hamoglobin. The plasma of the whole stored blood can be saved for other shocked patients, and the danger of transfusing potentially incompatible agglutinins is lessened. The concentrate is prepared from stored blood about ten days old. The red cells are allowed to sediment by gravity, then the plasma is pipetted off by suction apparatus and with it the "gel" which lies between the red cells and the plasma. This is formed mainly from the breakdown of leucocytes, fibrin deposit and platelets. It is thus possible to obtain 480 ml. of fluid which contains double the hæmoglobin concentration of two bottles of stored blood by pooling the contents of two bottles. One bottle of this cell suspension usually raises the hamoglobin 10 to 15 per cent. Normal saline should not be added as it increases the fragility of the crythrocytes.

"Plasmosan" transfusion.—The basic requirement of infusions for the treatment of shock is that it should restore the volume of circulating fluid. The colloidal component should have a molecular aggregate that will not readily escape through the vessel wall. It should be gradually excreted and should exert a colloidal osmotic pressure similar to that of the plasma proteins and should have a viscosity similar to that of blood. It should be safe and free from undesirable side-actions.

Polyvinylpyrrolidone is a white solid, very soluble in water and gives a clear colourless solution with a pH of 4·5-7. Laboratory studies have demonstrated that, in addition to compensating for the blood loss which results from massive acute hemorrhage, pyrrolidone solutions exert preventative and curative properties in traumatic shock. In 3·5 per cent. solution (500 mL) it has been widely employed for acute hemorrhage. It is concluded that the immediate use of plasmosan is an effective means of maintaining blood pressure.

Plasmosan is a sterile aqueous 8-5 per cent. solution of polyvinylpyrrolidone, together with electrolytes in proportions comparable to those in blood plasma. The solution is intended for intravenous infusion as an alternative to plasma, or as a supplement to whole blood.

Plasmosan is put up ready for use in 540 ml. waisted M.R.C. transfusion bottles. There is no necessity to warm or filter plasmosan before administration.

(The drawback to this method is that difficulty may be encountered in grouping on future occasions and possibly may affect ESR and clotting times.)

CHAPTER LII

DDT AND OTHER INSECTICIDES

DDT (dichlor-diphenyl-tri-chloroethane) is a colourless crystalline solid which is chemically stable, so that traces are very persistent. It is sparingly soluble in water. By no means unpleasant to use it is devoid of any disagreeable smell or colour and does not cause irritation or allergic effects.

Although it is lethal to a wide range of insects it is definitely not a ropellent. When particles come into contact with the insect's cuticle the poison is able to penetrate the integuments and cause the insect's death.

Gammexane (benzene hexachloride or BHC) exists in five isomers, of which one only, the gamma isomer, is highly insecticidal. Pure gamma, BHC, is a white crystalline substance, insoluble in water, but dissolving in organic solvents and to a small degree in mineral oil. It has a slight musty odour. Gamma BHC is absorbed by insects after contact or ingestion in a similar manner to DDT, but its action is quicker and is less porsistent than DDT as a residual film insecticide.

Chlordane (1068), octochlor or velsicol, is a chlorinated hydrocarbon compound with formula of C₁₀H_eCl₈ and possesses outstanding insecticidal properties. It is a viscous liquid with a faint odour and a slight tendency to crystallize. It is insoluble in water, but is miscible with many inorganic solvents, including deodorized kerosene.

New insecticides.—Some of these are chlorophenyl chloromethyl sulphone, the active principle of a German product "Lauseto Neu," or toxaphene (3956), DDD (dichloro-diphenyl-dichlorothane), methoxychlor, heptachlor, aldrin (compound 118) and dichdrin (compound 497). In addition there are certain new phosphorous insecticides, e.g., parathion, HETP (hexa-ethyl-tetraphosphate), "TEPP (tetracthyl-pyrophosphate), which are extremely toxic to some insects.

With the exception of Chlordane these insecticides are solid crystalline substances.

Application of DDT and BHC.—The essential requirement is the formation of small crystals or particles, $10-20~\mu$ in size which can easily be picked up on the feet of mosquitoes. For the preparation of wettable powders, or suspensions, it is necessary to grind the dust as finely as is required for the manufacture of paint. These very small crystals are more toxic if surrounded by a film of oil.

Deposits of solid particles of insecticides disappear rapidly from the surface of mud blocks made from laterite earths in E. and W. Africa, India and Jamaica.

Persistence is the most valuable property of DDT, so that surfaces contaminated with it will poison insects that rest upon them for many weeks, but, to bring DDT into contact with harmful species, it is necessary to spread a small quantity over a relatively large area. To do so, DDT is diluted with a solid in the form of powder, or with a liquid to form solutions, emulsions or suspensions. A good persistent result can be obtained by the use of about 0·1 mgm. DDT per sq. cm. A film of 0·01 mgm. BHC is

equally effective, but by no means so persistent. To apply a good deposit kerosene solutions containing 5 per cent, and 0.5 per cent, respectively are adequate. Gamma BHC is much more toxic than DDT and a mosquito invariably dies with a lethal dose after a brief contact period.

A comparatively simple type of film in anti-mosquito larval treatment is one in which a solution of DDT in oil is applied to the surface of water.

An oil with a high spreading pressure is necessary in order to form a powerfully spreading film over large areas despite aquatic weeds. A suitable oil (containing resin) should be sprayed here and there with a dosage of about 2 ml. per 100 sq. feet.

DDT and BHC can be applied against lice, fleas, pests of domestic animals, crickets and cockroaches in powders dispersed by means of a "dusting gun." In solution of 3–5 per cent. in kerosene producing a residual film they are used for bed-bugs and house flies. A coarse spray

is necessary.

They can be incorporated in paint or distempor, but the power is less than when applied direct. The crude DDT is broken up on a tile or concrete floor and, when pressure is applied, it produces a soft, sticky mass and is then made into a smooth paste. The powder should never be added direct to the bulk of oil. To prepare a 5 per cent, solution, \(\frac{1}{2}\) Ib. of fine powder is added to 1 gallon of kerosene or diesel oil. It is best to melt the insecticide gently and then pour it slowly into the kerosene with vigorous stirring. Suspensions are best made with the addition of some inert substance, such as kaolin, to assist floatation. A simple type is prepared by shaking a mixture of DDT, kaolin or tale with water containing soap. "Wettable" powders (50 per cent. DDT or 5 per cent. BHC) are available which contain the insecticide with a surface active agent.

Aërosol mists such as the aërosol bomb in which DDT is mixed with a liquid gas (dichlor-diffuor-methane - Freon) in a closed container. In the Freon bomb in Britain, carbon dioxide is used in small insecticidal sprayers. On opening a fine nozzle the liquid is driven out and forms a fine mist which has a transient insecticidal effect. The composition is:—DDT 3 per cent., lubricating oil 5 per cent., pyrethrine 0-3 per cent. dissolved in Freon. These aërosols, when released at 1-2 ft. from the ground level, can be used to put up a barrier around temporary camps.

Insecticidal smokes are clouds of insecticidal particles produced without

the agency of a carrier fluid. In use they are similar to aërosols.

Action on adult mosquitoes.—Generally speaking anopholines are more susceptible than culicines. DDT is used in sprays to augment pyrethrum and to ensure a quick "knock down." Such an anti-mosquito spray is 0.05 per cent. pyrethrum, with 5 per cent. sesame oil and 0.8 per cent. DDT in kerosene, and given at the rate of 1 fl. oz. to every 3,000 cu. feet. Sesame oil augments the insecticidal action of pyrethrums and also piperine derivatives, especially piperonyl butoxide. A synthesized product "Allethrin" has many properties similar to pyrethrum.

Pocket-size sprays can disperse insecticides with the following formula: 80 per cent. DDT, 20 per cent. cyclohexone, 5 per cent. motor oil, and

0.2 per cent. pyrethrum in kerosene.

Spraying of the internal surfaces of houses is the commonest method. Most anophelines enter houses to feed for 5-6 hours and then rest on walls and ceilings. Some, as A. darlingi in British Guiana, remain for two or three days; others such as A. albimanus and A. (Kerteszia) aquasalis for a few hours. Therefore spraying of houses once every 9-10 months with 5 per cent. DDT in kerosene, at a dosage of 100-150 mgm. per sq. foot, has practically eliminated malaria from British Guiana.

This method can only be used in certain types of houses. On absorbent materials, such as dried mud, serious losses of DDT and BHC solutions occur. Most health authorities now use wettable powder suspensions for large-scale operations. When applied by knapsack pressure sprayer at

doses of 100-300 mgm. per sq. foot, results are more permanent.

BHC possesses an initial toxicity to mosquitoes of Africa (A. gambice, A. funestus, A. moucheti) in the form of wettable powder. When applied at six-monthly intervals at a dosage of 13-15 mgm. gamma isomer per sq. foot it reduces the malaria parasite rate for children by 66 per cent. The same effect has been noted against A. minimus in Assam.

In Tanganyika experiments with BHC dispersible powder (P. 520) show that the lethal action persisted for three months against A, gambia which are killed before they have time to bite. The rate is 400 mgm. per sq. foot

in a mixture of 1 lb. in a gallon of water.

Residual outdoor spraying is of great value for mosquito destruction and leads to reduction of larvæ as well. When applied to walls of houses, barns and tents (in strength of 50–100 mgm. per sq. foot) it remains active for two months.

This depends largely on the habits of the mosquitoes. In New Guinea A. punctulatus enters houses for blood meals, but rests before feeding. Therefore, in this instance spraying of furniture and nets offers the best

chanco.

Action on mosquito larvæ.—Two to four ounces DDT per acre suffices to control anopheline or culicine larvæ. Application by drip can is less officient. The best solvents are kerosene or diesel oil No. 2. Adequate covering of the water is best obtained with 2 per cent. solutions at 2-8 quarts per acre.

In the case of stream breeders (A. minimus flavirostris in the Philippines) contact with larve is effected by sawdust impregnated with 2 per cent.

DDT solution.

Malariol (a special paraffin solution, see p. 98) with 5 per cent. DDT solution, half a gallon per acre, gives best control against anopheline larva. Spreading power is assisted by the addition of 0.25 per cent. resin.

A practical larvicide can be made of two parts of sawdust and one part of plaster of Paris by volume mixed with water and allowed to set. The mixture is then cut into pellets of ½-1 cm. and allowed to dry (48 hours). The pellets are then soaked in DDT in oil for a further 48 hours. Effectiveness is 100 per cent. for 2-4 weeks in suitable breeding places. The pellets are thrown for a considerable distance to breeding places which are difficult of access.

This method is specially adapted for ricefields where its use is harmless.

Aeroplane application.—The Stearman is the most suitable type. Solutions are used in 5 per cent, at the rate of 2–4 quarts per aero. The greater the concentration of the spray-fluid the greater the area that can be covered with aircraft. This measure has given good results in India, Burna and U.S.A., but in Italy, where the adult insects rest in houses and stables, results have not been so good. The fine liquid spray is effected through an emission tube, or venturi, under the fuselage, or through a boom with nozzles on the underside of the wings. Smokes or aërosols are produced by injecting the solution of insecticide into the exhaust stacks and relying upon the heat and exhaust to break it up into fine particles. Snecess is claimed from both. Best results are obtained at a height of 25–30 feet. An increase of pressure from 40–100 lb./sq. in. decreases the particle size from 145–90 μ which is important. One of the many problems to be solved is the adequate penetration of vegetation in order to kill anopheline larve.

Helicopters are employed to kill anophelines of the genus Kerteszia which breed in the axils of bromeliads. The effects are mainly due to the extermination of adult mosquitoes.

Action on sandflies (Phlebotomus).—The adult insects are highly susceptible, but the larve are resistant. Complete protection can be obtained by DDT or BHC residual sprays, attention being paid to corners and upper parts of the walls and doors, windows and screens. Outside spraying of walls, especially as in Turkey (where cow dung is plastered on) and rubble heaps dostroys sandflies before they can enter buildings. In Greece the standard method is by hand pressure sprays of watery emulsions of DDT (2 grm. per sq. m.).

The action of DDT and BHC on Simulidae.—The discovery that there exists a phoretic association of the pupe and larve of S. neavei with crabs in Kenya has a bearing on the application of DDT to rivers for the control of this important vector of onchocerciasis. It will now be necessary to treat only those rivers which are inhabited by this erab (Potamon niloticus).

The principles of DDT treatment is to apply an oil emulsion to the running water at the upper limit of the streams in sufficient quantity to maintain a concentration of at least 2 parts DDT per million parts of water for 30 minutes, repeating the process once every 10 days in order to kill successive batches of larve and checking the results for adult flies. The most successful was 20 per cent. DDT in toluene, with 10 per cent. soap and 1 per cent. "Abracol" as a stabilizer. The emulsion is applied from drip cans suspended over the water. Larvæ and pupe rapidly disappear and adult flies can no longer be caught one month after the start.

From January to February, 1951, seven applications were made at three-day intervals from fixed-wing aircraft of a DDT oil solution to vegetation on the banks of the Nile at Jinja. The results were highly satisfactory.

Action on house flies.—DDT acts only on the adults. It is used as a direct spray, or as a residual spray in breeding areas. In the direct spray the addition of 0.3 per cent. pyrethrum gives the necessary "knock

down." DDT dust is most effective in 1-2 grm. per sq. foot. On manure heaps DDT acts only if not covered up.

Action on tsetse flies.—DDT has to be sprayed twice a week on cattle in E. Africa as a means of controlling tsetse. No harm results to the cattle and a slow reduction in the flies has been reported. One per cent. solution in kerosene with addition of 5 per cent. gum leaves small crystals on the hairs which adhere to the feet of the flies. Especially susceptible are G. pallidipes, G. morsitans and G. swynnertoni.

Gamma BHC smokes have achieved considerable success against Glossina pallidipes and G. swynnertoni by fortnightly application in isolated blocks. Insectibar smoke (produced by T/FA generator) is now used for

dellying trains on the Mombasa-Nairobi railway.

DDT spread by aeroplanes has been carried out in Zululand (du Toit and Kluge, 1947). The area was sprayed three times over a period of five weeks. This procedure was adopted on the assumption that the first two applications would cover the normal gestation period of the flies. A 20 per cent. solution of DDT was dissolved in four parts of toluene oil and seven parts of C.I. fuel oil. This was fed at the rate of 5 gallons per engine per minute representing an output of 16 lb. DDT per minute. It was estimated that DDT would penetrate the dense foliage and be deposited on the undersurface of the leaves.

In September, 1950, seven applications were made from fixed-wing aircraft with 0.25 lb. DDT per acre at two and a half week intervals against G morsitans, G suprnertoni and G pallidipes. Rapid reduction of the fly populations was obtained and low densities persisted for six months.

Although total eradication was not achieved the tsetse fly incidence was

greatly reduced.

Action on bed-bugs.—These can be eradicated from buildings with BHC residual sprays in dosage of 200 mgm. per sq. ft. and when applied to mattresses, beds, and crevices prevents reinfestation for 6-9 months.

Action on reduviid bugs.—Gamma BHC is more effective than DDT. Dias and Pellegrino have used a watery emulsion in 1-2 grm. per sq. m. Adult bugs are more susceptible than nymphs, but on mud walls the toxicity is more effective. Smokes and aerosols are effective in houses in Argentina. Spraying with BHC (P. 530) in 7-5 per cent. suspensions in water has been employed against *Triatoma infestans* in Uruguay. After a nine months' interval the results are said to be satisfactory.

Action on cockroaches.—These are not so easy to control as they are very mobile and premises are so easily reinfested, though residual sprays constitute a valuable method of control. Dusting, 100 mgm. DDT, should be applied liberally. The German cockroach (Blatta germanica) is more resistant than the common species.

Action on lice.—DDT has completely revolutionized delousing policy.

Anti-louse powder contains 10 per cent. DDT. The chief advantage is that the individual can be treated fully clothed. Three treatments at

weekly intervals suffice for elimination of nits and lice. For mass treatment special dusting teams are organized. For head lice powder is applied direct to the head and nape of neck.

Impregnated clothing. Angola drab shirts are impregnated at the rate of 1 per cent. DDT weight for weight of garment. The shirts are referred to as A/T (Anti-typhus) and have proved most effective. If unwashed such a shirt affords complete protection for eight weeks and considerable protection for yet another four. Washing by a special process of the mobile laundry unit destroys the efficacy of DDT after the third washing.

For impregnation of garments the powder is insufflated by a blower into the loosened clothes. Of the various kinds the Dobbin (Superbilt) Duster or the Hudson (Admiral) are the best, though one of the horticultural types may be employed with the nozzle shortened to project about 8 in, beyond the barrel. The aim should be to insufflate powder mixed with air with an average of 11/2 oz. for each person. The head covering should be treated, and then, with arms extended, the delivery tube should be inserted into both sleeves and powder pumped between the skin and singlet, paying special attention to armpits and shoulders. Inserting the tube in front the chest should be sprayed from one side to the other. Next the tube should be inserted into the neck-band and the back should be dusted. The legs are treated through the trousers, especially the crutch and pubic areas. The waist, side seams and rear of pants are powdered in turn, especially over the buttocks and rear of the crutch. When no blower is available the powder can be well shaken into clothing removed from the body. The coat laid open on the table the whole inside and armholes are The trousers are treated in the same manner. By these means a team of two can treat 30 40 persons in an hour. The powder remains active for two to three weeks.

Prevention of noxious insects in aeroplanes. Regulations for quarantine disinfestation were developed in 1930. They require the use of an aërosol containing no less than 1 per cent. pyrethrins and 3 per cent. DDT at the rate of at least 5 grm, per 1,000 cu, feet. The typical formula is:—

Pyrethrum extract (20 per cent. pyrethrum)							5
DDT (percentage l	oy we	sight)			•	-	3
Cyclohexanone					•		5
Imbricating oil							2
"Freon 12"							

Disinfestation may be carried out whilst in flight, but must be accomplished at least half an hour before arrival. The ventilation system must be closed whilst the insecticide is released and for three minutes afterwards.

Action on ticks. The best results have been obtained with a water-dispersible powder P.580 (containing 6 per cent. gammexane). The action is high against ticks of sheep and eattle, and also against Argus, Orwithodorus and Boophilus.

Against Ornithodorus moubata in E. Africa Knowles and Terry advocate insecticide D.220, or agrocide 7, containing 2.5 per cent. gammexane,

one part, mixed with 4 parts of diatomite to produce a light powder, called G dust, applied at the rate of 3 lb. per 1,000 sq. feet. The results on sisal and other estates were not so striking as those in the townships. Here a different form of gammexane was used, D.034 or agrocide 3, which has a gamma gammexane content of 0.5 per cent. Regular treatment of houses achieved comparative freedom from O. monbata and almost complete elimination of tick-borne relapsing fever.

Toxic effects of DDT.—Some preparations of DDT under certain conditions do involve some risk to man. DDT distemper may be toxic and so are certain oily preparations. Fatal cases have been reported from drinking 5 per cent. solution in kerosene. The symptoms resemble those of carbon tetrachloride poisoning.

Resistance to DDT and BHC.—A significant development is the occurrence of resistance or tolerance in houseflies and in certain culicine mosquitoes. Other chlorinated hydrocarbon insecticides produce the same result, but a similar resistance has so far not been recorded in anopheline mosquitoes.

EPN, a phosphate compound (du Pont de Nemours Co.), controls mosquito larvæ and adult mosquitoes which are resistant to other insecticides. It is sprayed at 0.035 lb. per acre and is also suitable for plane dispersal. EPN is toxic to man and animals and has to be used with great care.

CHAPTER LIII

TABLE OF DRUGS FOR TREATMENT OF TROPICAL DISEASES

Composition, indications and dosages

This list has been drawn up in alphabetical order to afford ready assistance to the student and practitioner. In most cases the common or pharmaceutical name of the drug is given, with synonyms (in italics), chemical constitution, therapeutic application, dosage, spacing and other relevant information.

The Editor is indebted to Mr. R. Ferrier, M.P.S. of May and Baker, for

considerable assistance in this section.

Acetarsol B.P. Acetarsone, Fourneau 270, Kharophen, Orarsan, Oscarsan, Paroxyl, Spirocid, Storarsol.

3-acetylamino-4-hydroxyphenylarsonic acid.

Relapsing fever, Rat-bite fever, Trypanosomiasis, Yaws, Syphilis, Giardiasis, Balantidiasis.

Oral, 0.06-0.25 grm. (1-4 gr.).

Acetarsol Sodium. Storarsol-Sodium.

Sodium 3-acetylamino-4-hydroxyphenylarsonate.

Yaws, Syphilis.

Intramuscular or subcutaneous, 0.5 1.5 grm, (71 221 gr.).

Acetylarsan.

Diethylamine salt of acctarsol.

Yaws, Syphilis, Tropical Eosinophilia.

Intramuseular or subcutaneous, 1-3 ml, of 23·60° (1 ml, 0 05 grm, As).

Acidum Ascorbicum B.P. Vitamin C, Cevitamic Acid, Proscorbin, Redoxon,

Enolic form of 3-keto-1-gulofuranolactone.

Scurvy, Wound healing.

Oral, tab. acidi ascorbici 50 mgm. three times daily. Intravenous, in acute cases.

Acranil.

Hydrochloride of an acridine derivative.

Giardiasis, Balantidiasis.

Oral, tablets of 0.5 grm. Three tablets daily (1-5 grm.) for five days. Used in Germany and Scandinavia. No toxic effects. (See p. 540.)

Alepol. Sodium hydnocarpute, Sodium gynocardute.

Sodium salts of selected fraction of the acids of hydnocurpus oil,

Leprosv.

Subentaneous, intramuscular, intravenous, 1–10 ml, of 1 or 2% solution. (See p. 595.)

Anabin. Kurchi-bismuth-iodide.

Kurchi combined with bismuth iodide. Alkaloid is concessine (see p. 513).

Amorbinsis.

Oral, 0.25-0.65 grm. (4-10 gr.). Preparation used in India.

Aneurin. Aneurinæ Hydrochloricum B.P., Thiamine Hydrochloride, Vitamin B₁.
3-(4' Amino -2'-methylpyrimidine - 5'-methyl - 5-B-hydroxyethyl - thiazolum chloride hydrochloride.

Beriberi, Burns, Varicose Ulcers.

Oral, tablets 3 mgm. Injection, 25 mgm, in 1 ml. Store protected from light.

1

Anthiomaline.

Lithium antimony thiomalate.

Schistosomiasis, Lymphogranuloma inguinale, Leishmaniasis, Filariasis (W. bancrofti).

Intramuseular or intravenous, 0.03-0.12 grm. (\frac{1}{2}-2 gr.).

6% solution: 4 ml. for adult, 2 ml. for children.

On alternate days for 10 or more injections. (See p. 714.)

Anthisan. Menyramine maleate B.P.

A potent antihistaminic for the treatment of allergic conditions as in filariasis and schistosomiasis.

Oral, 0.3 grm. increasing to 1.0 grm. daily, in divided doses, taken only with food.

Antimosan. Von Heyden 661.

Potassium pyrocatechol-sulphonate. Contains 12.5 per cent. antimony in trivalent form

Kala-azar and other forms of Leishmaniasis.

Intravenous or intramuscular, 0.2 grm. (3 gr.). (See p. 159.)

Antrycide chloride. (Curd & Davoy, 1949.)

4-amino-6-(2'-amino-6'-methylpyrimidyl-4'-amino)-quinaldine-1: 1'-dimethochloride.

Trypanosomiasis of cattle and man.

Injection: single dose of 1 mgm. per kg. for Trypanosoma congolense. Similar activity for T. rhodesiense, T. brucci, T. evansi, T. equiperdum and T. equinum.

Antrypol B.P. Suramin, Bayer 205, Germanin, Fourneau 309, Moranyl, Naganol.

Urea of acid dimeta-aminobenzoyl-meta-aminoethyl-benzoyl-l-naphthylamino-4-6-8 trisulphonate of soda.

Trypanosomiasis (T. gambiense and T. rhodesiense). Onchocerciasis.

Intravenous, or rarely intramuscular, 1-3 grm. (15-45 gr.). Active in early stages of trypanosomiasis. (See p. 125.)

Areca, B.P. Betel Nut.

Dried ripe seeds of Areca catechu. Contains several alkaloids, the most active being arecoline.

Cestodiasis.

Oral, 1-4 grm. (15-60 gr.). Not so effective as Filix mas but is so in combination, with oleoresin of aspidium. May be used as a substitute. (See p. 815.)

Arsant.

A salvarsan compound in which two arsenic atoms are replaced by antimony.

Relapsing Fever.

Same doses as salvarsan.

Arsphenamine B.P. Arsenobenzene, Arsenobenzol, Arsenobillon, Arsenphenol-amine, Diarsenol, Ehrlich-Hata, or 606, Kharsivan, Salvarsan.

3:3'-diamino-4:4'-dihydroxy-arsenobenzene dihydrochloride.

Relapsing fever, Rat-bite fever, Yaws, Trypanosomiasis, Syphilis.

Intravenous, 0.3-0.9 grm. (5-15 gr.). (See p. 192.)

Ascabiol. Contains 25% benzyl benzoate in emulsion. Benzevan and Proscabin are similar preparation.

Benzul benzoate.

Scabies, Pediculosis (P. capitis and P. pubis).

Local application. (See p. 1008.)

Atepe.

Combination of atebrin 0.1 grm. and plasmoquine 0.005 grm. in each tablet for treatment of malaria.

Auremetine.

Combination of the periodides of emetine and auramine, containing 28% emetine, 16% auramine and 56% iddine.

Amorbiasis in chronic stage.

Oral, 0·12-0·2 grm. (2-3 gr.). (See p. 511.)

Aureomycin.

Antibiotic derived from Streptomyces aureofaciens,

Effective against numerous Gram-positive and Gram-negative organisms, Undulant fevers, Typhus, Q fever, Lymphogranuloma venereum, Psittacosis, Amœbiasis, Yaws, Coccidiomycosis.

Daily doses --oral - 60 mgm, per kg, in capsules of 250 mgm, three times daily for 5 days. Intravenous or intramuscular 3 mgm, per kg. (See p. 232.)

Avomine. 8-chloro-theophyllinate of promethazine.

Nausea, vomiting, travel sickness, cholera and other conditions,

Oral, tab. 25 mgm. (See p. 468.)

Azacrin. Amino-aza-acridine.

2 - methoxy - 6 - chloro - 9 - (5' - diethyl - amino - 2 - pentyl) - amino - 3 - aza - acridine dihydrochloride.

Malaria.

Oral, Tab. 0-4 grm. for 5 days.

Azo-arsenobenzol. (4197)

Trypanosomiasis,

Intravenous, 0.5 grm.

Bacitracin.

An antibiotic obtained from strains of *Bacillus subtilis*, not destroyed by blood, pus, or penicillinase. Indicated in Amoebic Dysentery. Topical application in sterile saline or as an ointment.

Oral, 500 units per grm. Intramuscular, 80,000 units for 10 days. Intravenous injection contra-indicated.

BAL (Sec Dimercaprol.)

Berberine sulphate B.P. Orisol.

Oriental sore.

Subentaneous or as ointment, 0.06-0.3 grm. (1-5 gr.).

Betanaphthol, B.P.

B-naphthol.

Ancylostomiasis, Ascariasis, Cestodiasis,

Oral, 0.2-0.65 grm. (2-10 gr.).

Bismosol.

10% solution of potassium sodium bismuthotartrate (containing 0.3% piperazine) in glucose solution.

Syphilis, Yaws.

Intramuscular, 0.1 ml. (1.7 min.).

Bismuth arsanilate.

Syphilis, Yaws.

Intramuscular, 0.06 grm. (1 gr.).

Bismuth oxychloride. Injectio B.P.

Yaws.

Intramuscular 0.06-0.2 grm. (3 gr.).

Butarsen. 70A (Eagle).

P-arsenoso-phenyl-butyric acid.

Used in trypanosomiasis.

Camoquine. Amodiaguin, Miaguin, CAM-AQ1, S.N. 10751.

Malaria.

Oral, 0.2 grm. of base as bihydrochloride. Adults 0.6 grm., children 0.4 grm., under five 0.2 grm.

Carbarsone. Amebevan, Amibiarson, Leucarsone.

4-carbaminophenylarsonic acid.

Yaws, Americanis,

Oral, 0.25 grm. (4 gr.) or per rectum, 2 grm. (30 gr.). (See p. 513.)

Carbon Tetrachloride, B.P. Tetraform, Tetrachlormethane.

Ascariasis, Ancylostomiasis, Cestodiasis, Trichuriasis.

Oral, 3 ml. (45 min.). (See p. 808.)

Cestodin, Nematodin,

Metallic tin, oxide and chloride.

Costodiasis.

Oral tablets 1, t.d.s. (See p. 817.)

Chaulmoogra Oil B.P.

Oil expressed from seeds of Hydnocarpus kurzii.

Oral, intradermal, subcutaneous or intramuscular, 0.3-5 ml. (6-85 min.). (See p. 695.)

Oil of Chenopodium, B.P. Oil of American Wormseed.

Oil distilled with steam from fresh flowering and fruiting plants of Chenopodium ambrosioides var. anthelminticum. Contains 65% W/W of ascariodole.

Ascariasis, Trichuriasis, Ancylostomiasis.

Oral, 0.2-1 ml. (3-17 min). (See pp. 807, 817.)

Chiniofon B.P. Anayodin, Dysentulin, Quiniosulphan, Quinoxyl, Yatren.

Sodium-7-iodo-8-hydroxy-quinoline-5-sulphonate.

Amcebiasis, Bacillary Dysentery.

Oral, 0.06-0.5 grm. (1-7½ gr.). Per rectum, retention enemata 2½-3% solution. 1-5 grm. (15-45 gr.). (See p. 511.)

Chloromycetin. Chloramphenicol.

Antibiotic isolated from Streptomyces venezuelue isolated from soil.

Typhus fevers, especially Mite typhus, Typhoid, Bartonellosis.

Intramuscular or intravenous injections 1-5 grm. daily. (See pp. 231-240.) Oral, capsules 250 mgm., three times daily for 6 days.

Chloroquine. Aralen, Resochin, Nivaquine B, Tanakán. S.N. 7618, 3377 R.P., Chloroquin A.C. (Winthrop-Stearne).

Malaria and Hepatic Amcebiasis. Hymenolepis nana, Trichuris trichiura, Balantidiasis. (See p. 87.)

Oral, or injection.

Suppressive. 0.3 gramme once a week.

Curative. First day 3 doses each 0.3 gramme followed by one dose of 0.3 gramme daily for 3 days. Powerful schizonticide. Side-effects, pruritis of hands. (See p. 87.)

Cinchona. Cinchona Febrifuge.

Mixed cinchona alkaloids in varying proportions.

Malaria.

Oral, 0.06-0.6 grm. (1-10 gr.) two or three times daily.

Used as a substitute for quinine. (See p. 83.)

Compound 6257

Condensation product of sulphathiazole and formaldehyde.

Cholera.

Oral, 6 grm. Total dosage 28 grm. Rectal administration advised. (See p. 466.)

Crystal Violet B.P. Gentian Violet, Methyl-rosaniline.

Hexamethylpararosaniline hydrochloride.

Oxvuriasis, Cestodiasis (Hymenolepis nana), Clonorchiasis.

Oral, 18 mgm. per kilo for 10–20 days. Total dosage in elonorchiasis 1·2 grm.; in oxyuriasis 0·5 grm. t.d.s. for 7 days. (See pp. 796, 817.)

Daraprim. Pyrimethamine, Malocide (Fr.)

5 (p-chlorophenyl)-2: 4-diamino-6-cthylpyrimidine.

Malaria, especially benign tertian.

Oral, 10-20 mgm. or more daily; 5 mgm. daily suppressant.

DDT (dichlor-diphenyl-trichlorethane) insecticide. (See pp. 861-866.)

Diamino-diphenyl-sulphone.

DDS, or DADPS.

Leprosy, Mycetoma.

Oral, tablets 100 mgm. twice weekly. (See p. 592.)

Diasone. Promanide.

4: 4-diaminodiphenyl sulphone disodium formaldehyde sulphoxylate. Derivative of diaminodiphenyl sulphone.

Leprosy, Tuberculosis.

Oral or intravenous. Daily doses up to 2 grammes. (Sec p. 593.)

Dimercaprol. B.P. Synonym BAL (British Antilewisile).

Indicated in metallic intoxication due to heavy metals: gold, arsenic, mercury, antimony and bismuth. Compounds effective against trypunosomes and spirochates are divided into two groups according as to whether or not they are inhibited by BAL. Those which are inhibited are metal-containing compounds, but this property is not exercised in respect of anti-bacterial action. BAL inhibition of toxicity towards the parasite does not depend upon the same mechanism as BAL inhibition of toxicity towards the host.

Ossage. Issued in ampoules containing 100 mgm. of active substance. The following desage by intramuscular injection into the glutei: 1st day, 100 mgm. 4 times at 4-hourly intervals; 2nd, 3rd and 4th days, 100 mgm. morning and evening; 5th and 6th days, 100 mgm. daily.

Diodoquin.

Diiodohydroxyguinoline, Dihaloguin, Embeguin, Savorguin.

Contains 63.9% iodine.

Chronic Amobiasis.

Oral, tablets 0.25 or 0.3 grm. (4 gr.), 3-10 daily for 10 days, especially for sterilizing cyst carrier cases. (See p. 513.)

Diphenan B.P. Butolan, Oxylan.

p-benzylphenylcarbamate.

Oxvuriasis.

Oral, 0.5 grm. (74 gr.) three times daily.

Dithranol B.P. Anthralin, Anthrarobin, Cignolin, Derobin.

1:8-dihydroxyanthranol.

Oriental sore, Ringworm skin affections.

As an ointment, 0.25-3%. (See p. 676.)

Egressin. N-isoamylcarbaminic acid-3-methyl-6-isopropyl-ester.

Oxyuriasis, Ascariasis.

Oral, for children, in ices. Three doses of 1 grm. children: 2 grm. adults.

Emetine and Bismuth Iodide B.P., E.B.I.

Bismuth iodide of emetine.

Amobiasis.

Oral, 0·12-0·2 grm. (2-3 gr.). Total 20-30 gr.

In gelatin capsules for chronic intestinal amœbiasis. (See p. 510.)

Emetine Hydrochloride B.P.

(Emetal is a solution of emetine base in olive oil).

Amobiasis.

Subcutaneous or intramuscular, 0.06 grm. (1 gr.), usually given in daily doses.

Total 6-12 gr. Has powerful effect on acute symptoms, but does not cure the chronic infection or prevent "carriers."

Emetine Periodide B.P., E.P.I.

Periodide of cmetine.

Amorbiasis.

Oral, 0·2-0·6 grm. (2-6 gr.). For chronic amorbiasis. Less toxic than E.B.I. (See p. 511.)

Eparseno.

Dioxy-diamido-arsenobenzol.

Leishmaniasis, Espundia.

Intramuscular, ()·12-0·25 grm.; 10-20 injections at intervals of three days.

Etharsanol.

Sodium 4-\$-hydroxycthylaminophenylarsonate.

Trypanosomiasis (T. gambiense).

Intravenous, 2 grm. (30 gr.). (See p. 127.)

Ethyl Esters of Hydnocarpus Oil B.P. Antileprol, Chaulmestrol, Hydnestryle, Moogrol.

A mixture of the ethyl esters of the unsaturated fatty acids (chiefly chaulmoogric and hudnocarpic acids) of hydnocarpus oil.

Leprosy.

Intradermal, subcutaneous or intramuscular, 2-5 ml. (34-85 min.). (See p. 525.)

Folic Acid. Pteroylglutamic acid.

Synthetic product resembling Lactobacillus casei factor of liver and yeast

Produces hamopoietic response in macrocytic anamia.

Tropical sprue, Nutritional Tropical Macrocytic Anæmia.

()ral, 5-30 mgm. (See p. 559.)

Fouadin. (See Stibophen.)

Fourneau 710, Plasmocide, Rhodoquine.

G-methoxy-8-diethylamino-n-prophylaminoquinolene.

Malaria.

Oral, as for pamaquin.

Furnagillin. Antibiotic isolated from Aspergillus fumigatus.

Amobic dysentery. Active on cultures of E. histolytica 1: 10 million. Oral, 50-125 mgm. per kg.

Gammexane.

Gamma isomer of Benzene hexachloride insecticide.

Oral, Oxyuriasis (under trial). Ointment, ½ per cent. Scabies.

Halarsol.

3-amino-4-hydroxyphenyl-l-dichloroarsine hydrochloride.

Yaws, Ameebiasis

Intravenous and intramuscular, 0.2 grm. (3 gr.).

Helminal.

A dry extract prepared from a sea alga, a species of Digenea.

Ascariasis, Cestodiasis,

Oral, 3-0:25 grm. (3-4 gr.). Preventive; of doubtful value.

Hetrazan (8 (L.). Banocide, Notezine, Diethylearbamazine.

1-diethulcarbamul-4-methul piperazine hydrochloride, Hetrazan citrate.

Filariasis (W. bancrofti, W. pacifica, Loa loa, Onchocerca volvulus, Mansonella ozzardi and Dipetalonema perstans). Larva migrans, Ascaris tumbricoides.

Oral, 0.5-2 mgm, per kg, body-weight three times daily.

Hexamine B.P. Aminoform, Formamine, Formin, Methonamina, Metramine, Urisol, Uritone, Urotropine, Vesalvine.

Hexamethylene tetramine.

Urinary infections (Bact. coli.), Cholecystitis

Oral, 0.6-2 grm, (10/30 gr.).

Hexylresorcinol, B.P. Caprokol.

1: 3-dihydroxy-4-hexylbenzene.

Ascariasis, Ancylostomiasis, Oxyuriasis, Trichuriasis.

Oral; also I in 2,000 solution rectal enema for oxyuriasis. Pills of 0.2 grm. (3 gr.) 5 daily. (See p. 810.)

Holarrhena B.P. Kurchi, Coorchi.

Contains the alkaloids conessine, holarrhenine, kurchicine and kurchine.

Amorbiasis.

Oral, 0:25/0:6 grm. (4/10 gr.). Preparation used in India.

Hydnocarpus Oil B.P.

Fatty oil obtained by cold expression from seeds of Hydnocarpus wightiana.

Intradermal, subcutaneous or intramuscular, 2 5 ml, (34-85 min.). (See p. 595.)

Injectio Bismuth B.P. Bisglucol, Bismostab.

20% W/V precipitated bismuth 0.5% V/V cresol in isotonic dextrose solution.

Yaws, Syphilis.

Intramuscular or deep subcutaneous, 0.5 1 ml. (0.1 0.2 grm. Bi.) (8-17 min.). (See p. 618.)

Injection of Bismuth Salicylate B.P. Bisantol, Bismosan,

10% suspension of bismuth salicylate in neutral regetable oil.

Yaws, Syphilis.

Deep intramuscular or deep subcutaneous, 2 ml. (34 min.) (1 ml. 0.057 grm. Bi). (See p. 618.)

Isopentaquine. (See Pentaquine.)

Kaolin Leve B.P. Light kaolin. Bolus alba.

Oral, 200 grm. in 400 ml. of water.

Mist Kaolini et Morphinæ. Light kaolin 30 gr., sodi biearb. 10 gr., tinet. chloroformi et morphinæ 10 min., water to 1 oz.

Kikuth's Sdt. 386B.

Arseno-stibio compound of the salvarsan type.

Bartonellosis.

Intravenous, 0.2 grm. (3 gr.). (See p. 218.)

Kousso. Cusso.

Kusotoxin, active principle. Dried female flowers of Brayera anthelmintica.

Cestodiasis, T. saginata, in Abyssinia.

Oral "Koussein." 1-4 grm. (15-60 gr.) in divided doses at half-hour interval. Total dosage 4-8 grm. (60-120 gr.) followed by purgative. Effective if freshly prepared. (See p. 817.)

Male Fern, B.P.

Ether extract of dried rhizome and leaf bases of Dryopteris filix mas containing 25% W/W filicin.

Cestodiasis.

Oral, 3–5.5 ml, (60–90 min.) in gelatin capsules followed by saline aperient. (See p. 815.)

Mandelic Acid B.P.

a-hydroxy phenylacetic acid, phenylglycollic acid.

Urinary infections, especially Bact. coli.

Oral, 2-4 grm. (30-60 gr.) daily. Usually necessary to give more than one course.

Mandelix.

Elixir of ammonium mandelate containing the equivalent of 3 grm. (45 gr.) of mandelic acid in 2 dr.

Urinary infections, especially *Bact. coli*. 5i (3·3 ml.), three times daily for 10 days.

Mapharside. Mapharsen.

3-amino-4-hydroxyphenyl-arsenoxide hydrochloride.

Malaria, Trypanosomiasis, Syphilis, Yaws. Intravenous, 0.05 grm. (3 gr.). (See p. 127.)

Melarsen. Arsobal (Specia France), 4289.

d-sodium salt of triazine arsinic acid.

Trypanosomiasis (T. gambiense).

Early cases cured by I dose of 4 mgm. per kg.

Melarsen B.

Combination with BAL. (See Dimercaprol.)

Trypanosomiasis. Penetrates C.N.S.

Melarsen-oxide.

Trivalent compound of Melarsen.

Trypanosomiasis (T. gambiense).

Intramuscular or intravenous injection of 25 mgm. daily. Oral 150 mgm.

MSb and MSba

Antimonial analogues of Mclarsen and Melarsen oxide (Friedheim).

Mepacrine hydrochloride B.P. Atabrine, Atebrin, Acriquine, Chemiochin, Chinacrin, Crinodora, Erion, Italchina, Malaricide, Quinacrine, Metoquine, 2-chloro-5 (w-dicthylamino-a-methybutylamino)-7-methoxyacridine dihydrochloride.

Malaria, Giardiasis, Cestodiasis, Oriental Sore, Lupus crythematosus.

()ral, ()·05 ()·1 grm. ($\frac{3}{4}-1\frac{1}{2}$ gr.) initial dose as high as 0·2-0·3 grm. (See p. 90.)

Mepacrine methane-sulphonate B.P. Atebrin musonate, Quinacrine soluble.

Dimethanesulphonate of mepacrine.
Malaria, Giardiasis.

Intramuscular or subcutaneous, 0.05-0.1 grm. (2-12 gr.). (See p. 90.)

Merthiolate. Thiomersalate B.P.

Sodium ethylmercurithio-salicylate.

Ringworms.

Local application, 0.1%. (See p. 680)

Mesulphen B.P. Mitigal, Sudermo (Contain 25% of sulphur).

2:6-dimethylthianthrene.

Scabies, Ringworm of feet.

Local application. Made up in standard solution.

Milibis. Wid.

Bismuth derivative of oxy-para-N-glycolyl arsanilate. Contains 15:01 per cent. arsenic: 41:81 per cent. bismuth.

Amorbic Dysentery,

Oral, tablets 250 mgm, three times daily 7-16 days. (See p. 513.)

Miracil D. Nilodin, Thioxanthone, Tixantone. Lucanthone hydrochloride. B.P.C. Hydrochloride of 1-methyl-4-beta-diethyl-aminathyl, aminothioxanthone.

Schistosomiasis.

Oral, 300 mgm, at twelve hour intervals up to 14 days. (See p. 716.)

Myocrisin.

Sodium aurothiomalate.

Relapsing fever, Lymphogranuloma inguinale, Clonorchiasis,

Deep subcutaneous or intramuscular, 0.01 0.05 grm. († † gr.); continue with 0.1 grm. († † gr.) at weekly intervals.

Neoarsphenamine B.P. Neoarsaminol, Neo-arsenobenzolum, Neoarsenphenolamine, Neodiarsenol, Neosalvarsan (Ehrlich 914), Novarsan, Novarsenobenzene, Novarsenob

Sodium 3:3'-diamino-4:4'-dihydroxy arsenobenzene-N-methylene sulphoxylate,

Relapsing fever (S. duttoni and S. recurrentis), Rat-bite fever (S. minus), Yaws, Syphilis, Malaria, Kala-azar, Trypanosomiasis, Tropical Eosinophilia, Intravenous, 0-15-0-9 grm. (2‡-15 gr.).

Neocryl.

Sodium succinanilo-methylamide-p-arsonate.

Trypanosomiasis, Syphilis.

Intravenous, 1.5 grin. (221 gr.) (See p. 127.)

Neo-halarsine.

Arsphenoxide tartrate.

Trypanosomiasis, Syphilis, Yaws.

Intravenous, 0.09 grm. (11 gr.). (See Mapharside.)

Neo-premaline.

An association of Chloroquine ()·15 gramme, Praquine ()·0075 gramme and Rhodoquin 0·0075 gramme.

Malaria.

Oral.

Suppressive, two tablets once a week.

Neostam. Stibamine glucoside, Pentostam.

Nitrogen-glucoside of sodium p-aminophenylatibinate.

Kala-azar, Oriental Sore, Espundia.

Intravenous, 0.2 grm. (3 gr.). (See p. 171.)

Neostibosan. Bayer 693B, von Heyden 693.

Diethylamine-p-aminophenyl-stibinate.

Kala-azar, Oriental sore, Espundia.

Intravenous or intramuscular, 0.2 grm. (3 gr.). (See p. 159.)

Nicotinic acid B.P. Niacin.

Pyridine-3-carboxytic acid.

Pellagra.

Oral, tablet 50-250 mgm. daily; also intravenous.

Nicotamidum B.P. Nicotinic acidamide Niacinamide.

Pyridine-3-carboxylic acidamide.

Pellagra.

Oral, tablet 50-250 mgm, daily.

Oleoresin of Aspidium.

Contains filicin.

Costodiasis.

Oral, -3 in emulsion. (Sec p. 815.)

Paludrine (4888). Proguanil, Chlorguanide, Diguanil, B.P., Guanatol, Drinupal, Palusil, Trian, Chloriguane, S.N. 12837.

N₁-p-chlorophenyl-N₂-isopropylbiquanide acetate, lactate, and monohydrochloride.

Malaria, all forms.

()ral, ()·1-()·75 grm. (11-12 gr.) daily, 7-10 days. Prophylaetic, 0·1 grm.

Pamaquine, B.P. Beprochin, Plasmochin, Plasmoquine (simplex). Præquine, (lamefar, Quipenyl, Aminoquin (6-methoxy-8 (4-diethylamino-1-Methylbutylamino) quinoline).

Malaria.

Oral, 0.02-0.04 grm. $(\frac{1}{3}-\frac{2}{3}$ gr.) daily for 7 days. (See p. 87.)

Pamaguine-Compound. Plasmoquine-Compound.

Quinine sulphate and pamaquin in the proportion of 12.5 to 1.

Malaria

Oral, 0.125 grm. (2 gr.) quinine, 0.01 grm. (4 gr.) pamaquin.

Para-amino-benzoic acid. P.A.B.A.

Typhus.

Oral, 12 grm.

Pelletierine tannate, B.P.

A mixture of tannates of the alkaloids obtained from pomegranate stem and root bark (Punica granatum), the chief of which are pelletierine and pseudo-pelletierine. (Extediusis.

()ral, ()·12-0·5 grm. (2- $7\frac{1}{2}$ gr.). Used as a substitute for Filix mas.

Penicillin B.P.

The sodium potassium or calcium salt from *Penicillium notatum*. Procaine penicillin has more lasting effect (0·3-0·6 mega units daily). Penicillin aluminium monostearate (P.A.M.) recommended by W.H.O. for Yaws. *Bicillin* effective for 2 weeks (N,N'-dibenzyll ethylene diamine dipenicillin G.), also Penicillin G. (Neopenil) diethylaminoethyl ester hydriodide.

Staphylococcal, streptococcal, gonococcal, pneumococcal, and other grampositive infections, and for the treatment of Syphilis, Yaws, Ulcus Tropicum, Relapsing Fevers, Leptospirosis and Rat bit fever.

Intramuscular injection, I mega unit twice daily. Calcium salts used by mouth

and for topical application.

Pentamidine isethionate M. & B. (M. & B. 800).

4: 4-diamidino-diphenoxy-pentane di-(β-hydroxethane sulphonate). Lomidine (Fr.) is pentamidine dimethanesulphonate. In these compounds 1 mgm, of base equals, 1-21 mgm, of the dihydrochloride; 1-74 mgm, of the di-isethionate; and 1-56 mgm, of dimethane sulphonate (lomidine).

Trypanosomiasis, Kala-azar, Espundia.

Inframuscular, 4 mgm. per kg. body-weight dissolved in 3–4 ml. of water, Injections can be given daily or on alternate days. A course consists of not less than 12 injections. May also be given intravenously, but this is frequently followed by a rapid fall in blood-pressure with sometimes the alarming symptoms of collapse. For the prophylaxis of trypanosomiasis 175 mgm. are given at six months' intervals.

Pentaquine. S.N. 13,276

(6 methoxy-8 (5-isopropylamino amylamino) quinoline)

Malaria.

Oral. Used in place of Pamaquin being claimed to be more active and less toxic.

Dosage the same as Pamaquin. Isopentaquine and primaquine are also similar.

Phenothiazine. Phenovis. (See also Reconnox and Contraverm.)

Thiodiphenylamine.

Ascariasis, Oxyuriasis, Dracontiasis.

Oral, 4-8 grm. (60-120 gr.) spaced over 4 days. May be dangerously toxic in children. Injected in oily solution in 1 grm. doses in vicinity of guinea-worm.

Phthalylsulphathiazole. Thalistatin, Thalazole.

Bacillary dysentery, Ulcerative colitis, Infantile gastroenteritis, Chronic amobie dysentery, Pre- and post-operative use in intestinal and rectal surgery.

Oral. Average adult dose in bacillary dysentery 3 4 grammes daily. Much higher doses used in surgery.

Piperazine hydrate. Antepar clixir.

Oxyuriasis.

In syrup for children. 50–75 mg, kg, per day. $\frac{1}{3}$ gr, daily per year of life.

Potassium Antimonyltartrate B.P. Tartar emetic, Emétique.

Kala-azar, Oriental Sore, Espundia, Yaws, Lymphogranuloma inguinale, Try-panosomiasis, Relapsing Fover, Lepra reaction, Schistosomiasis, Filariasis, Intravenous, 0-03-0-12 gcm. (½ 2 gr.) alternate days, up to total of 40 gr.

Premaline.

An association of Mepacrine ()-10 gramme, Rhodoquin ()-005 gramme and Pamaquin ()-005 gramme.

Malaria.

Oral

Suppressive, three tablets once a week.

Primaquine. (See Pentaquine.)

Promin.

Sodium p, p-diamino-diphenyl sulphone-N-N-didextrose sulphonate.

Leprosy, Tuberculosis.

Intravenous, 2 grammes daily gradually increased by 1 gramme until a maximum dosage of 5 grammes is reached. This is continued for long periods if necessary.

Promizole.

4: 2-diaminophenyl-5-thiazolyl phenyl sulphone.

Leprosy, Tuberculosis.

Oral, daily doses up to 6 grammes.

Propamidine.

4: 4' Diamino-aw-diphenoxypropane di (B-hydroxethane sulphonate).

Leishmaniasis, Kala-azar.

Intramuscular, the same doses as pentamidine and has the same actions. Active against various bacteria. Used as ophthalmic solution and as a cream.

Proparsanol.

Monosodium salt of 3-p-arsono-anilino-proponol.

Trypanosomiasis (T. gambiense).

Intravenous, 2 grm. (30 gr.). (See p. 127.)

Quinidine Sulphate, B.P.

Cinchona alkaloid isomeric with quinine.

Malaria.

Oral, 0·2-0·6 grm. (3-10 gr.). In same dosages as quinine for benign tertian.

Quinine Bisulphate, B.P.1

Malaria.

Oral, 0.06-0.6 grm. (1-10 gr.) two to three times daily.

Formula is as for hydrochloride but $\rm H_2SO_4$ instead of HCl. Easily soluble in water.

Quinine Dihydrochloride, B.P.

Malaria.

Oral, intravenous and intramuscular, 0·3–0·6 grm. (5–10 gr.) two to three times daily. (See p. 86.)

Formula as for hydrochloride but with two HCl instead of one.

Quinine Ethyl Carbonate, B.P. Quinine, Euchinine.

Malaria.

Oral, 0:1-1:0 grm. (1\frac{1}{2}-15 gr.). Tasteless compound almost insoluble.

Quinine Hydrochloride, B.P.

Malaria.

Oral, 0.66-0.6 grm. (1-10 gr.) two to three times daily. (See p. 82.)

Quinine Sulphate, B.P.

Malaria. Night cramps.

Oral, 0.06-0.6 grm. (1-10 gr.) in solution with dil. H₂SO₄. (See p. 82.)

Formula as for hydrochloride but with \(\frac{1}{2} \) H₂SO₄ instead of HCl.

Quinine and Urethane, B.P. Injection.

Sterile aqueous solution containing quinine hydrochloride 13:33%, wrethane 6:67%.

Malaria.

Intravenous or intramuscular, 5 ml. Has been used for painless intramuscular injection. (See p. 84.)

Quiniplex.

Benign Tertian Malaria.

Oral, tablets containing 150 mgm. Quinine sulphate, plus 6.5 mgm. pentaquine phosphate, 6 daily for 14 days or longer prevent relapses.

Reconnox. Phenothiazine compound, Contraverm.

Oxvuriasis.

Oral, tablets 0.2 grm. (see p. 983).

¹ Formula of quinine is (6: methoxy-a 15-vinyl-2-quinadidyl)-4-quinoline methanol.

Riboflavin. Vitamin B2, Lactoflavin, Vitamin G, Riboflavina. B.P.

d-riboflavin: 6: 7-dimethyl-9-d-ribityl-180-alloxazine.

Pellagra.

Oral, tablets 5-10 mgm. daily.

Rivanol.

2-ethoxy-6: 9-diaminoacridine lactate.

Ameebiasis, Chronic bacillary dysentery.

Oral, 0.1 grm. (1½ gr.). Per rectum retention enemata 0.1%, usually given in 1:500-1:2,000 solution.

Rubiazol. Rubiazol injectable.

2: 4 diamino 6-carboxyazobenzene 4'-sulphonamide.

Fungous infection of feet.

Local application, 5% solution.

Santonin, B.P.

Santonica, dried unexpanded capitula of Artemisia maritima, var. anthelminticum. Ascariasis, Oxyuriasis.

Oral, 0.06-0.03 grm. (1-5 gr.). Usually prescribed in combination with calomel. (See p. 799.)

Silver Arsphenamine B.P. Silver Arsebibenzol, Silver Salvarsan.

Sodium salt of silver arsphenamine.

Syphilis, Yaws.

Intravenous, 0.1 0.6 grm. (11 10 gr.).

Simaruba B.P.

Dried root-bark of S. amara (Simarubacee), "Mountain Damson." Infusion of 15 gr. to 1 ounce of boiling water for 15 minutes.

Dysentery, bacillary and amobic.

Oral and rectal retention enemata, 1/2 grm. (15/30 gr.). Astringent. Has been used in both chronic amorbic and bacillary dysenteries.

Sobita (Howards).

Sodium bismuth tartrate.

Yaws. (See p. 618.)

Intramuscular, 0-2 grm. in 10% solution 2 ml.

Sodium Antimonyltartrate B.P.

Sodium Antimony Tartrate.

Schistosomiasis, Kala-azar, Oriental Sore.

Intravenous, 0:03-0:12 grm. (§ 2 gr.). (See p. 712.)

Sodium thiacetamide. Arsenamide.

p-p(bis-(carboxy-methyl-mercapto)arsino) benzamide.

Filariasis. W. pacifica.

Intravenous, in 2 per cent. solution, 1 mgm. per kg. daily for 15 days. (See p. 766.)

Solganal B.

Aurothioglucosc.

Relapsing fever, Lymphogranuloma inguinale, Clonorchiasis,

Intravenous or intramuscular, 0.1-0.4 grm. (11 6 gr.).

Soluseptasine. M. & B. 137.

Disodium-p-(y-phenylpropylamino)-benzenesulphonamide-a-y-disulphonate.

Filarial lymphangitis.

Intramuscular injection. 10 ml, of 5% solution. Number of injections uncertain. Solustibosan. Sdt. 561. Stibatin, Stibanose. Sodium antimony gluconate, Pentostam.

A pentavalent antimony compound of hexonic acid.

Kala-azar, Oriental Sore, Espundia,

Intravenous or intramuscular, 6 ml. containing 2% antimony, (0·126 grm.). A course of 10 daily injections; well tolerated. (See p. 160.)

Soluthiazole.

Disodium- $2(p-(\gamma-phenylpropylamino)benzenesulphonamide)$ thiazole a: γ disulphonate.

For Parenteral sulphonamide therapy by intravenous or intramuscular injection. A 45 per cent. solution corresponding to 20 per cent. of sulphathiazole and in adults intravenous doses of up to 5 grammes of sulphathiazole (25 ml. of Soluthiazole solution) may be given. In less acutely ill patients two injections of 5 ml. separated by 4 hours have been found to give good results.

Solvochin.

A 25% water soluble basic quinine preparation for intramuscular injection with plI adapted to reaction of tissues; dissolved in phenazone.

Malaria.

Intramuscular, 2·2 ml. twice daily for 4 days. Each ampoule contains 0·5 grm. (7½ gr.) quinine. Causes little local reaction. (See p. 84.)

Sontochin. S.N. 6911, 3038 R.P., Sontoquine, Santoquine.

(7-chloro-4 (4-diethylamino-1 methylbutylamino)-3-methylquinoline) disulphate and monohydrate salts.

Malaria.

Dosage and action the same as chloroquine.

Stabilarsan.

Arsphenamine diglucoside.

Yaws, Syphilis.

Intravenous, 0.3 grm. (5 gr.).

Stibamine.

Sodium p-uminophenylstibinate.

Kala-azar.

Intravenous, 0·1-0·2 grm. (½-3 gr.); total dose, 6-10 grm. On alternate days.

Stibophen B.P. Foundin, Nevantimosan, Reprodal, Fantorin.

Sodium-antimony-bispyrocatechol 3: 5-sodium disulphonate. Contains 13.5 per cent. antimony in trivalent form.

Schistosomiasis, Lymphogranuloma inguinale, Leishmaniasis, Undulant fever, Filariasis.

Intravenous and intramuscular, 0.1-0.3 grm. $(1\frac{1}{2}-5$ gr.) in 7% solution, 1.5 ml., 3.5 ml., 5 ml. on consecutive days. Then 5 ml. on alternate days. Total 40 ml. (See p. 715.)

Stibosan, Von Heyden 471.

Sodium-m-chlor-p-acetylaminophenylstibinate.

Kala-azar, Rat-bite fever.

Intravenous or intramuscular, 0.2 grm. (3 gr.). Total dose 6-10 grm. On alternate days. (See p. 159.)

Stilbamidine, Diamino-stilbene. M. & B.741, Diamidino-stilbene.

4.4' diamidino-stilbene.

Used in the form of the β -hydroxyethanesulphonate.

Kala-azar.

Intravenous, Indian kala-azar; 0-04, 0-075, 0-09, 0-12, 0-14, 0-15 grm. single course of 10-15 daily injections. Children: initial dose of 0-015 grm. Sudan kala-azar; 1-5 to 3-5 mgm. per kg. body-weight. Fifteen daily injections separated by 7-day intervals. Total dosage: 3-4-88 grm. (For complications see p. 161.)

Streptomycin. Dihydrostreptomycin.

An antibiotic isolated from Actinomyces grisens, chiefly employed as the sulphate,

Meso-1-3-dignanidino-2, 3, 4, 6 tetrahydroxy-cyclorexane glucoside of a
disaccharide.

Active almost entirely against gram negative organisms, being both bacteriostatic and bactericidal.

"Q fever," Plague, Tukaremia, Ulcerating Granuloma of Pudenda, Bacillary Dysentery, Bact. coli infections.

Intramuscular in solution 0.5 grm, twice daily.

Oral, in eachets, 4 grm. daily for 7 days for intestinal infections,

Succinyl Sulphathiazole B.P. Sulphasuxidine, Colistatin.

2-(p-succinyl-amino benzenesulphonamido) thiazole,

Bacillary dysentories, Ulcerative colitis.

Oral, 10 14 grm. (150 210 gr.). Initial dose 4 grm. followed by maintenance dose of 2 grm. 4 times daily. Total amounts vary from 27.5 120 grm. Daily in six doses for 10 17 days (1942). American workers advocate large doses: 0.25 grm. per kilo body weight, followed by daily maintenance dose of same strength.

Sulphadiazine B.P.

2-(p-aminobenzenesulphonamido)-pyrimidine.

Pneumonia, Malaria, Plague, Filariasis, Lymphogranuloma inguinale, Meliodosis, Oral, 1–4 grm. (15-60 gr.): initial dose 4 grm. followed by 1 grm. every four hours. The least toxic member of the group.

Sulphadimidine B.P. Sulphadimethylpyrimidine, Sulphamezathine,

2 (4-aminobenzenesalphonyl-amino-4: 6-dimethylpyrimidine).

Pneumonia, Bacillary dysentories, Ulcerative colitis.

Oral, 8-10 grm. (120-150 gr.). Daily for 5-7 days.

Sulphaguanidine B.P. p-aminobenzenesulphonylynanidine monohydrate.

Bacillary dysenteries.

Oral, 5-20 grm, (75-300 gr.). Opinions vary on optimum dosage. Many consider dosages advocated too large. (See p. 488.)

Sulphamerazine. Sulphamethylpyrimidine.

For systemic sulphonamide therapy. Bact. coli infections.

Oral. For acute infections in adults, 3-4 grammes followed by 1-0 gramme every 8 hours. This should be continued until obvious clinical response. For children from 3-10 years, 1-5 gramme followed by 1-0 gramme every 12 hours; 6 months to 3 years, 1-0 gramme followed by 0-4 gramme every 12 hours; under 6 months, 0-5 gramme followed by 0-25 gramme every 12 hours. These doses may be increased in severely ill patients up to 50 per cent.

Sulphanilamide B.P. Ambesid, Colsulanyde, Lysococaine, Prontosil Album, Prontylin, Rubiazol-A, Stramid, Streptocide, Sulfamidyl.

p-aminobenzenesulphonamide.

Malaria, Undulant fevers, Streptococcal infections, Meningococcal meningitis.

Locally for wounds.

Oral, 0.5-1 grm. (8-15 gr.) 6-8 grm. daily for courses of 5-7 days. Not so effective as and more toxic than sulphathiazole and sulphadiazine.

Sulphapyridine. Dagenan (M. & B. 693), Eubasinum, Sulphidine.

2-(p-aminobenzenesulphonamido)-pyridine.

Lymphogranuloma inguinale, Madura foot, Bubonic plague, Streptococcal infections, Pneumonia, Gonorrhea, Cerebrospinal meningitis.

Oral, 0.5-2 grm. $(7\frac{1}{2}-30$ gr.) followed by 1 grm. 4-hourly for 2 days. Then 1 grm. 6-hourly for 2 days.

Sulphapyridine soluble. Dagenan-sodium (M. & B. 693 soluble).

Mono-hydrated sodium salt of sulphapyridine.

Filariasis, Lymphogranuloma inguinale, and other infections as above.

Intramuscular or intravenous, 0 06 grm. per kg. body wt. 2-4 grm. (30-60 gr.). Number of injections uncertain.

Sulpharsphenamine B.P. Kharsulphan, Metarsenobillon-M.A.B., Myosalvarsan, Sulfarsenol, Sulpharsenobenzene, Sulphostab.

Disodium-3: 3'-diamino-4: 4'-dihydroxyarsenobenzene-N: N'-dimethylene sulphate.

Relapsing fever, Yaws, Syphilis, Trypanosomiasis.

Intramuscular or deep subcutaneous, 0.1-0.6 grm. (11-10 gr.).

Sulphathiazole B.P. Ciba 3714, Thiazamide (M. & B. 760).

2-(p-aminobenzenesulphonamido)-thiazole.

Pneumonia, Malaria, Plague, Filariasis, Lymphogranuloma inguinale.

Oral, 2 grm. (30 gr.) initially; 1 grm. every 4 hours.

Sulphatriad.

An association of sulphathiazole 0.37 grm., sulphadiazine 0.37 grm. and sulphamerazine 0.26 grm. per grm. for systemic sulphonamide therapy with reduced risk of crystalluria.

Oral. As for other active sulphonamides.

Sulphetrone.

Tetrasodium-4-41-y-phenylpropyl-amino-diphenyl sulphone tetra-sulphone.

Leprosy, Tuberculosis.

Oral, 6–9 grm. daily with an initial dose of 1·5 grm. daily and gradually increased. (See p. 592.)

Sulphone Cilag.

Mono-acetyl-ester of D.D.S.

Leprosy. (See p. 593.)

Sulphoxyl-Salvarsan.

Sodium-diamino-arseno-antipyrine-mono-N-methylene-sulphoxylate.

Relapsing fever.

Intramuscular or deep subcutaneous, 0·3-0·6 grm. (5-10 gr.). (See p. 192.)

Teropterin.

Ptercyltriglutamic acid.

Sprue (see p. 559).

884 TABLE OF DRUGS—TROPICAL DISEASES

Terramycin. Oxytetracycline.

An antibiotic isolated from cultures of Streptomyces rimosus.

Amediasis, Typhus Fevers, Salmonella infections. Pact. coli infections. Oxyuriasis, Balantidiasis, Ulcus Tropicum, Yaws.

2 gm, daily by mouth in divided doses, or 0.5–1 gm, daily intravenously in divided doses. Tablets of 0.25 grm, each.

Tetrachlorethylene, B.P.

Ethulene tetrachloride.

Ancylostomiasis, Oxyuriasis, Hymenolepis nana.

Oral, 3 ml. (51 min.). (See p. 809.)

Tetraethyliurammonosulphide.

Tetmosal for Scabies. When combined with soap in 5 to 20 per cent, dilution, it retains its sarcopticidal properties (Gordon et al. 1944).

Thiacetazone. Thioparamizone.

p-cetylaminobenzaldehyde thiosemicarbazone.

Tuberculosis and leprosy.

15-mgm, tablet daily, gradually increased to 3 or 4 tablets daily.

Thio-bismol.

Sodium salt of bismuth thio-glycollic acid.

Benign Tortian Malaria.

Intramuscular injection 0.2 grm. (See p. 93.)

Thymol, B.P.

3-methyl-6-isopropylphenol.

Anevlostomiasis.

Oral, 3 4 grm. (45-60 gr.). Not much used.

Totaquina, B.P. Panchina, Chineto.

Mixture of cinchona alkaloids containing not less than 70% crystallisable alkaloids of which not less than one-fifth is quinine.

Type I. Quinine, einchonine, einchonidine, no quinidine.

Type 11. Quinine, quinidine, cinchonine, cinchonidine.

For composition as given by Chopra see p. 83,

Malaria.

Oral 0.06-0.6 grm. (1-10 gr.) two to three times daily for indefinite periods.

Treparsol. Formyphenarsine.

Sodium formyl-m-amino-p-oxyphenylarsonate.

Syphilis, Amorbiasis.

Oral, 0.25 grm. (4 gr.).

Trichlorethylene, B.P. Chlorylen, Westrasol.

Ancylostomiasis, Oxyuriasis,

2-3 ml. (34-51 min.). (See p. 809.)

Triostam.

Sodium antimonyl gluconate.

Trypanosomiasis:--Schistosomiasis, S. hæmatobium and S. mansoni. Six per cent. solution. Intravenous 15-20 mgm. per kg. Six-day course. Adult man 60 kg., dosage 200 mgm. for 6 days. Oral, enteric-conted tablets.

Trivalent sodium antimony gluconate. SAG.

Schistosomiasis.

Intravenous, 180 mgm. for 6 days. Solution must not be heated.

Tryparsamide B.P. Tryparsone, Tryponarsyl, Trypotan, Novatoxyl, Glyphenarsine.

Sodium-N-phenylglycineamide-p-arsonate, Acetyl-p-amino-o-oxyphenyl arsenic acid.

Trypanosomiasis (T. gambiense and T. rhodesiense), Neurosyphilis. Intravenous or intramuscular, 1-2 grm. (15-30 gr.). (See p. 126.)

Urea Stibamine. Stiburea.

A combination of urea and p-aminophenylstibinic acid.

Kala-azar.

Intravenous or intramuscular, 0.2 grm. (3 gr.). (See p. 160.)

Vioform. Enterovioform.

Iodochlorhydroxyquinoline.

Chronic Amœbiasis.

Oral, 0.25 grm. (4 gr.). Pills, 4 daily for 5 days; subsequently smaller amounts. Much used in India and in America. (See p. 513.)

Vitamin B 12. Bitevan, Cytamen, Distivit, Normocytin.

Pernicious anæmia, Nutritional macrocytic anæmia, Tropical Sprue and Macrocytic anæmia of pregnancy.

Intramuscular injection 50 μ mgm.

APPENDIX

SECTION A. MEDICAL ZOOLOGY

I. Medical Protozoology

PLASMODHDÆ, (Malaria Parasites.)

The number of known species of plasmodium in man and animals is about 120. Four species occur in man: Plasmodium vivax, P. ovale (p. 889), P. malariæ (p. 888) and P. falciparum (p. 890). Closely allied organisms have been found in apes and monkeys. P. pitheci in the orang outang (Pongo pygmaus) somewhat resembles P. malariæ. Hepatocystis kochi and P. gonderi occur in Cercopithecus, P. knowlesi, which is a commensal in Macaca irus, the "Kra Monkey," produces a fatal infection in 99 per cent. when inoculated into Macaca mulatta. P. knowlesi produces Schuffner's dots like P. vivax. P. cynomolyi, also a parasite of Macaca irus, closely resembles P. rivax. P. reichenowi, which resembles P. falciparum and produces crescents, has been discovered in the chimpanzee and gorilla.

The only instances of human malaria being transferred to other mammals are those of Taliaferro who produced transient infection with P, falciparum in the red howler-monkey (Alouatta seniculus) in South America; while Rodhain succeeded in infecting the chimpanzee with P, rivax by intravenous inoculation with 16 ml, of defibrinated blood. The crythrocytic forms can maintain themselves for a few weeks. P, schwetzi, the natural parasite of the chimpanzee is easily passed from animal to animal and is morphologically identical with P, rivax.

The European mosquito, Anopheles maculipennis atroparcus, is an efficient carrier of P. cynomolgi, and, although monkeys have been successfully infected by the bites of these mosquitoes, the same batch of insects failed to produce the disease in man. Some successful inoculations of man with certain species of monkey parasites have been recorded. Knowles and Das Gupta, followed by other workers, have, on many occasions infected man with P. knowlesi, but by direct blood inoculations only. P. gonderi and P. inui have also been passed to man.

These experiments, though few in number and relating to only three species of monkey parasite, provide scientific evidence that at least some species of parasites belonging to the lower monkeys are able to produce infection in man, at least under artificial conditions.

A number of malaria-like parasites have recently been described from rodents. Of these the most important are *P. berghei* from the tree rat, *Praomys jackson*, of the Belgian Congo and *P. vinckei*, Rodhain, from *Thannomys surdasteri* The insect vector in both is *Anopheles dureni*. The infection is easily passed to rats, mice and to the cotton rat. In these animals it causes heavy parasitemia and death from the eleventh to fifteenth days. Liver and spleen are greatly enlarged and, like *P. vivax*, infected red corpuseles are grossly enlarged. Field and Edeson have described *Hepatocystis russali malayensis* in four species of squirrel (*Callosciurus*) in Malaya, whilst recently *P. brodeni* has been described from the African elephant shrew, *Elephantulus rufescens dundasi*. Birds have a number of malaria-like parasites, others have been recorded in bats and squirrels, and even lizards. *P. relictum* and *P. cathemerium* are present in sparrows and other birds. *P. lophura*, a parasite of

Pekin ducks, has been much employed for chemotherapeutic studies. Elongated schizonts and gametocytes rather resembling P. falciparum are found in P. circumflexum. Avian intracorpusclar parasites are transmitted by culicine mosquitoes, as a rule, but also by anopheles. In the avian red blood corpuscle Plasmodium displaces the cell nucleus, thus differing from Hamoproteus, a common blood parasite of tropical finches, which is transmitted by a hippoboscid fly, Lynchiamunu. An interesting side-light on the development of plasmodiide in the vertebrate host has been shed by the discovery of a plasmodium of fowls, Plasmodium gallinaceum, which produces pigmentless schizonts in the endothelial cells of capillaries of the brain, kidney, lung, liver, heart and bone-marrow, constituting the exoerythrocytic (E.E.) cycle, and similar stages have been found in P. clongatum, P. relictum, P. cathemerium of the canary, and in P. lophuræ of the duck.

This is the result of studies in tissue-culture by Hawking and in chicks inoculated with sporozoites of P, gallimaceum from the salvary glands of Acles egypti, which transmits this parasite. They are detectable in the intercellular spaces, but soon become oval or spheroidal parasites in the macrophage cells, and the mature schizonts make their appearance from the thirty-sixth to the forty-eighth hour, When liberated they enter other macrophages and wander widely. The second generation are known as the metacryptozoites, some of which enter crythrocytes. After the second generation all organs become infected. About the fifth day a type of schizont appears which gives rise to large numbers of small micromerozoites in contrast to the earlier generation with smaller numbers of macro-merozoites (Huff and Coulston, 1915).

This cycle was found for the first time in the endothelial cell in a mammal (bat) by Mer (1947) and shortly afterwards in a cercopithecus monkey (Garnham), but these latter parasites belong to a new genus, *Hepatocystis*, and are now known as *H. mawinum* and *H. kochi* respectively. The E.E. cycle has been demonstrated by Shortt and Garnham in *P. cynomolgi*, but not, as yet, in *P. knowlesi*, though apigmented cryptomerozoites have been demonstrated by Shortt and Garnham in the human liver in the case of *P. rivax* and *P. falciparum*.

Pigment-producing parasites in the blood cells of certain reptiles are either Harmoproteus or Plusmodium.

Benion Tertian. (Plasmodium vivax) (Pl. IIB, facing p. 36)

In the early stages the parasite is ring-shaped, measuring $(2-4\mu)$ one third the diameter of the containing corpuscle.

The nucleus is large, situated at the thinnest part of the ring. (It is sometimes duplicated to form two dots which represents the original structure broken into two fragments). As the ring grows, so the corpuscle enlarges and Schüffner's dots are formed. At thirty hours, the trophozoite becomes amoboid whilst hemozoin is being deposited in the cytoplasm in the form of pigment. The extruded pseudopodia explain the great irregularities in the contour seen in unstained specimens (Fig. 3, p. 35), but movement ceases directly the parasite has attained maximum size. The nucleus divides in thirty-six hours; the parasite may now be 10-12µ in size and the host cell twice as big as normal, but the vacuole in which the nucleus is situated, and which is filled with chromatin, becomes smaller as the parasite develops. At 40 hours it is nearly fully matured. Schüffner's dots are chromophilic particles which stain with Romanowsky's stain. At first fine, they soon become coarse and more prominent and characteristic of P. vivax and P. ovale. Sometimes the infected red corpusele is twice normal size, and usually the rim surrounding the parasite has a washed-out appearance.

Schizogony.—The fully formed schizont is almost round, larger than the diameter of a normal corpuscle, nearly 9 or 10µ in diameter. The nucleus is at first fairly large, lying near the periphery, with chromatin diffusely arranged; one or two small vacuoles may be present. Multiplication proceeds by repeated division of the nucleus, followed by segmentation of the protoplasm, the result

of which is a malberry-shaped mass. The number of merozoites thus formed varies from 14 to 24, the average being about 16. The complete cycle occupies 48 hours, but the process of active multiplication varies from 6.8. Completed schizogony coincides with the appearance of rigor in the malarial subject (Fig. 3, p. 35.)

Gametogony. When schizogony has proceeded for a certain period the young trophozoites become sexual forms (or gametocytes). In the immature stages they are difficult to distinguish from schizonts of a similar age, but soon they can be recognized as small, solid forms. Growth is much slower, the gametocyte taking nearly twice as long to mature as a schizont. No vacuole develops in the evtoplasm, ; it is less active, and hence fails to exhibit the manifold changes in form seen in the growing schizont. Pigment is produced in greater quantities, being more evenly distributed without clumping. The macrogametocyte (or female form) is much larger than the mature schizont, being 12–14 μ in diameter, whilst the microgametocute (or male form) is much smaller (Fig. 4, p. 35). Other distinguishing features in the microgametocyte are the large diffuse nucleus spreading across the body in the shape of a spindle, and the hyaline protoplasm, which stains a pinkish blue. The nucleus of the macrogametocyte is small, compact and stains more deeply; the cytoplasm is granular, non-vacuolated and stains intense blue. As a rule macrogametocytes are more numerous in the blood than are microgametocytes. Both appear in the blood in about six days, but do not mature for forty-eight hours; they probably also develop in the hone marrow. (Mosquitoes may be infected as early as the seventh day, but in artificially-produced blood infection it may be as early as the fourth day.) For description of pre- and exo-erythrocytic cycles, see p. 900.

P. vivax is capable of maintaining itself (after a single infection) in the human body for a maximum period of about three years, but it usually dies out sooner.

QUARTAN (Plasmodium malariae) (Pl. 11C, facing p. 35)

This parasite has a localized and patchy geographical distribution. Its chief characteristics are the mildness of the febrile attacks which it occasions and its ability to produce relapses over a long period. The parasite is more solid than other species and produces quantities of dark pigment. It is, therefore, the pigmented parasite. It is usually scanty in the peripheral blood. Quartan has a cycle in the peripheral blood of 72 hours. The ring, or young trophozoite, usually

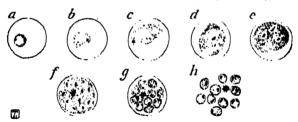


Fig. 216. Quartan parasite, asexual cycle: stained.

has a signet-ring appearance, and resembles that of $P.\ www.$, but is usually more solid. Amoboid movement is feeble, so that the irregular forms frequently seen in benign tertian are not found in quartan infections. Later still, when fully pigmented, amoboid movement ceases (Fig. 216). The parasite then has a sharp outline and frequently grows across the corpuscle, producing a ribbon or bandshaped appearance. The nucleus is large and tends to be elongated. The pigment is usually deposited at the periphery of the parasite.

The host cell is not enlarged, but may contract and become somewhat smaller. Schüffner's dots are not produced, but stippling (Ziemann's), consisting of small and less distinct fine dots and points, can be revealed by special Romanowsky staining. The pigment is dark brown and coarse, and the oscillation of individual granules less mark d than in *P. vivax*.

Schizogony.—The fully developed schizont is distinctly smaller than the corresponding phase of P. vivax, rarely exceeding 6.5μ , and the parasite does not occupy the whole red cell. Nuclear division commences after the schizont has been growing for 48 hours and proceeds slowly. The number of merozoites is small, from 6 to 12, symmetrical in arrangement, producing a daisy-head appearance. The individual merozoites are larger than in P. vivax and average 1.75μ . These segmenting forms are more frequently seen in the peripheral blood than the corresponding phase of other parasites.

Gamelogony.—The growing gametocytes do not assume the band form of the growing schizont. The young macrogametocyte is heavily pigmented and contains a smaller quantity of chromatin than the schizont of the same size, but the microgametocyte has more chromatin, a band-shaped nucleus, faintly-staining protoplasm and completely fills the corpuscle. It is a curious point that gametoeytes of both sexes are particularly scanty in the blood. On the whole, the microgametocyte is slightly smaller than the macrogametocyte. The quartan parasite lives longer in the peripheral blood than the benign tertian, and persists for six, or even as long as twenty-one years (see p. 52). According to Shute and Maryon this species is difficult to transmit by Anopheles maculipennis atroparrus, but 1. slephensi is a much more efficient carrier. The occysts differ from those of other human species of *Plasmodium* (Fig. 226). Up to the sixth day the pigment is coarse and resembles that of *P. falcipurum*, but after that date a marked clumping of the pigment is observed. The intrinsic incubation period in man of the quartan parasite is never less than 20 days (Shute); in most it is between 21-59. It would seem that the average is 30 days and therefore the tissue phase in the liver should be longer than in P. rivax or in P. falciparum. The sporozoites are longer and broader than those of P. vivax and P. falciparum and contain more chromatin.

Pre-crythrocytic and exo-crythrocytic cycles.—The E.E., or tissue cycle of P. malariæ, has not yet been worked out. Garnham worked with P. inui, a parasite of Mucaca irus which resembles P. malariæ very closely and is regarded as the analogue of that parasite in monkeys. Pre-crythrocytic schizogony was observed in the liver from the seventh to twelfth days. The earliest stage was $5.5~\mu$ in diameter with five nuclei: the most mature about $22~\mu$ with over 2,000 merozoites. Pseudocytomere formation is a prominent feature. As compared to similar stages in P. cynomolyi growth is slow.

OVALE TERTIAN (Plusmodium ovale), Stephens, 1922 (Pl. 11D, facing p. 35)

This species was discovered by Stephens in 1922 in a patient from East Africa, though previously described in 1914 by Ahmod Emin at Camaran (Red Sea). Yorke and Owen (1930) showed that the morphological features were maintained when the parasite was transmitted by direct blood inoculation, and later James and Shute succeeded in transmitting it through Anopheles maculipennis. It is, therefore, a distinct and constant species. It has a much wider distribution than was formerly thought, through Central, West and East Africa to Egypt and South Africa. Cases have been notified from Turkmenistan, Palestine, Philippines, Mauritius, Egypt, India and Venezuela.

P. ovale has several features in common both with P. vivax and P. malaria.

It produces, like the former, a tertian periodicity; there is some enlargement of the host cell to $10\,p$, and Schuffner's dots are present. On the other hand, the parasite more nearly resembles P. malariw.—It may best be described as a quartan parasite in a benign tertian cell, or a round parasite in an oval cell. The pigment is not so heavy as in quartan. The small rings have no special features, but lie in red blood corpuscles, which are usually oval with fimbriated margins (hence the specific name of the parasite). Early stippling of red blood corpuseles containing rings is a feature of this parasite. Half-grown forms are non-amerboid: the pigment is granular and brownish-black. The amount of chromatin and the distribution of pigment in a lateral band recall the quartan but, unlike the latter, "band forms" are not so common. The mature schizonts do not quite fill the host cell. The maximum number of merozoites may be twelve; usually it is eight, and they are enclosed in a decolourized degenerated corpusele with many Schüffner's dots; occasionally two parasites are seen within one cell. The chromatin of the merozoites is crescentic and may bear accessory dots. The clinical course of the infection in man is usually mild and the parasite tends to die out after several paroxysms. (The maximum is about seven.) For this reason it is not very effective in therapeutic malaria. The paroxysm of fever produced by this parasite takes place towards the evening or at night.

P. ovale takes longer than benign tertian to develop in anopheles—15 as against 10 days. The character and arrangement of the pigment in the occyst in the stomach wall of the mosquito is distinctive and the sporozoites in the salivary glands are distinctly smaller than those of other species of plasmodium (Figs. 219, 224). In the Editor's experience P. ovale may persist in the body for two years without manifesting itself, despite the fact that the patient may have been treated for other varieties of malaria.

Subtertian or Malignant. (Plasmodium falciparum) (Pl. 11A, facing p. 35)

Synonym. Laverania malariw. A notable feature in the identification of this parasite is its much smaller size; the rings average $1\cdot 25$ to $1\cdot 5$ μ , about $\frac{1}{6}$ the size of the corpusele. Older rings may be indistinguishable from those of other species in size, but early phases, owing to their minute size and the narrowness of the cytoplasm, may be difficult to see (Fig. 217a). The rings are usually sharp and regular. The nucleus is often divided into two, which may serve to

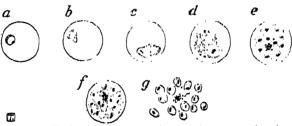


Fig. 217. -Evolution of the subtertian parasite: asexual cycle.

distinguish it from similar forms of the benigh tertian. Multiple invasion of the corpuscle is often encountered and is very characteristic; it is doubtless due to the prodigious number of parasites present. Another characteristic of the young subtertian parasite is its tendency to apply itself to the margin or edge of the corpuscle—usually known as "accolé" or "appliqué" forms. They may appear

² The pre-crythrocytic stages of P. orale have been described by Garnham and colleagues (1954) in the liver of a volunteer. On the ninth day the mature schizouts resemble those of P. maturine more than those of P. water.

as short streaks with red nuclear dots, giving them a bacilliform appearance (Pl. III, facing p. 37) and may be difficult to recognize. Clumping of red blood corpuscles is frequently observed in blood-films and is reminiscent of flocculation in blood grouping. The parasitized cells are surrounded by non-parasitized crythrocytes.

As development proceeds, the invaded corpuscles are filtered out by the capillaries and small arteries of the viscera and bone-marrow. They are specially



Fig. 218.—Trophozoites of P. falciparum showing Maurer's clefts in erythrocytes. × 1,000. (Microphotograph by Dr. J. Bell.)

numerous in the spleen and liver. In heavy infections, a few more mature forms may be seen; very occasionally a fully-segmenting schizont. On rare occasions all stages of schizogony may be observed in the peripheral blood, and in these prognosis is usually grave. The ring forms disappear before pigment is seen. As a rule, it is necessary to aspirate splenic blood, puncture the sternum or search the viscera (especially the liver or spleen) immediately after death, in order to demonstrate the more advanced stages of the parasite (Fig. 217, c, d, e, f). The whole cycle of schizogony is probably 36 to 48 hours. The size of the host cell remains unaltered. Schüffner's dots do not occur, but usually a few brick-red loops, streaks or dots, larger and more irregular in shape than Schüffner's are seen; these are known as "Maurer's clefts." (Fig. 218.) The loops are commoner with larger rings. In the fresh state the infected corpuscles have a slightly darker appearance, resembling old brass, hence they are often called "brassy bodies." Pigment in the growing schizonts occurs in well-developed blocks, usually appearing as one dark conspicuous mass.

Schizogony takes place within the capillaries of the internal organs. The fully-formed schizont measures $4.5-5~\mu$ in diameter, so that it occupies only two-thirds of the red-cell. The number of merozoites (even with a single infection) varies from 8 to 32 (Fig. 217, g). The merozoites, much smaller than in other species, average 0.7 to 1 μ . Schizogony does not proceed at a uniform rate and may vary from 36-48 hours. The forms in the internal organs are small and solid

without vacuoles. The pigment is jet black and forms a single central mass, and on this account is apt to be mistaken for the quartan.

Gametogony. The gametocytes assume the very striking crescentic shape (Fig. 4, p. 35), but this description is not quite correct, for the ends are not pointed but more banana-shaped. (Fig. 219.) They are fairly large bodies, from 9 to 14 μ by 2–3 μ in breadth. A definite capsule appears to be secreted round the mature crescent (gametocyte). Crescents are not seen at the onset of the infection, but once

Fig. 219. Formation of male gametocyte (crescent) of P. falciparum, > 1,000. (Microphotograph by Dr. J. Bell.)

they appear in the peripheral blood, they tend to increase in numbers during the next few days. They are less amenable to the action of quinine and atebrin than other stages of the parasite, and may persist in the blood for six weeks after subsidence of the fever; individual erescents have a life-span of 30 60 days. It has been noted that quinine administered at the commencement of a subtertian attack prevents the appearance of crescents. They are rapidly extirpated by plasmoquine (pumaquin) (p. 87) and paludrine, but are not affected by atchrin (menacrine) or quinine. Two sexes of crescents can be distinguished. The male (microgametocyte) is broader and more stumpy than the female; the nucleus is diffuse and occupies the greater part of the protoplasm, and the pigment is scattered throughout the protoplasm and the cytoplasm is often pinkish blue when stained by Romanowsky stains. The female (macrogametocyte) is more slender and possesses a small centrally-placed nucleus with the pigment concentrated round it. When the crescent is fully matured, the protoplasm of the corpuscle is completely engulfed, so that only the corpuscular envelope persists and may be distinguished as a phantom outline. Sometimes twin or double crescents have been seen in one corpuscle. It has often been remarked that in the most severe clinical types of subtertian malaria in Western and Central Africa crescents are few and in some instances cannot be found in blood-films, whereas in these same African infections, when examined later in England, they may be numerous,

In primary infections croscents appear in the peripheral blood with clocklike regularity on the tenth day after the onset of fever; by the fifteenth they

have reached their maximum. If they have not appeared by the twelfth day they are unlikely to do so later. Female gametocytes can often be found two days before the males. Crescents are produced from specialized merozoites in the internal organs, but especially in the blood sinuses of the bone-marrow. The immature gametocytes are distinguished from schizonts of the same age by their clongated shape as well as by the scattered arrangement of the pigment. At first the nucleus is small, and is placed towards one end of the body, usually extending as a cross line one edge in the same way as the quartan. Subsequently the nucleus becomes centrally placed. In a large series of cases Shute and Maryon found that gametocytes developed in 55 per cent., especially those which recrudesced or relapsed after administration of sub-therapeutic doses of antimalarial drugs which appear to stimulate the production of sexual forms. The female gametocytes appear before the male and persist long after the latter have disappeared. The gametocytes develop from asexual parasites present in the blood during remissions.

P. falciparum has a much shorter lifespan in the human body than other species. A single infection survives from one month to one year. Short term relapses may be very frequent, every two or three weeks over a period of one year or less, in the absence of adequate treatment. There are no long remissions or long term relapses as in P. vivax.

Strains of *P. falciparum* appear to differ greatly in virulence and in their susceptibility to antimalarial drugs, especially to quinine. According to Shute, some tropical strains cannot be transmitted through *Anopheles maculipennis* var. alroparvus, although this species is an efficient carrier of European strains of *P. falciparum*. Shute has proved that strain of *P. falciparum*, which develops readily in indigenous *Anopheles m. atroparvus* in the Roman Campagna, but when these insects are taken to West Africa they prove refactory to infection in that area, but the same parasite develops readily in the laboratory in *Anopheles slephensi*, and a Roumanian strain does the same.

Morphological varieties of P. falciparum are thought to exist. A form with large rings is found in Africa and it has been claimed that blackwater fever does not occur with the small ringed form, but is associated solely with the former and is more often accompanied by Maurer's dots. Small hair-like rings are characteristic of a primary infection.

 $P.\ tenue$, occasionally seen in India and Africa, has been regarded as a subspecies. This has large rings; "tailed" forms are seen in 10–12 hours, then there are "spider-web" stages, with tiny, spidery pseudopodia interlacing the corpuscle. Accolé forms are exceptional. That this is a variety of $P.\ falciparum$ is to be inferred from its association with typical crescents.

The pre-erythrocytic cycle of P, falciparum has been described by Shortt, Fairley, Covell, Shute and Garnham in a human volunteer subjected to liver biopsy. Numerous mosquitoes—A. maculipennis atroparvus and A. quadrimaculatus—were infected from a patient harbouring gametocytes of P. falciparum. They were fed on the volunteer for three days in succession in the course of which 770 bites were recorded. The results were assessed 140 hours after the initial feed, when it was expected that the tissue forms would be found at three stages of development separated by twenty-four hours. These were found in the parenchyma cells of the liver. In shape they are oval and lobose. The fourth day form measured about 31 μ by 26 μ , the fifth day 50 μ by 36 μ , the sixth 60 μ by 30 μ . The number of nuclei is much greater than in the case of P. vivax and increases with age. The oldest (140 hours) were in process of segmentation and some of them were already releasing small merozoites (0·7 μ across) into the sinusoids. In some an apparent membrane was present around the schizonts, but they did not provoke any cellular reaction. The pre-erythrocytic forms

resemble those of *P. civax* and *P. cynomolgi*, but the mature schizont is considerably larger, whilst the merozoites are smaller and more numerous. Schizogony proceeds more rapidly. This similarity indicates that these three species are closely related.

Abnormal malaria parasites. -Frequently, in the tropics, in hyperendemic areas, mixed infections of two, more rarely three, species of parasites may be found in the same individual. The usual combination is that of the benien tertian with the subtertian. Immature forms of both parasites may be demonstrated in the same microscopic field, but more usually various developmental stages of the benign tertian are seen with subtertian crescents; still more infrequently the two different species have been recorded within the same cell. In Ceylon and Malaya combined infection of benign tertian and quartan are not uncommon. Ever since the time of Schaudinn, certain puzzling appearances. especially in benign tertian infections, have been noted which were thought by him to denote a process of parthenogenesis, but it was recognized (J. D. Thomson) that this mulberry-like mass really consisted of a segmenting schizont and a gametocyte confined within a single red blood-corpusele. Combined infection of schizont plus male or female gametocyte, or even twin gametocytes, have frequently been recorded. Multiple infections with two, three or even five subtertian rings are commonly seen in heavy infections.

Cultivation of malaria parasites. Cultivation in vitro of malaria parasites was first accomplished by Bass (1911) and has since been amply confirmed. Asexual multiplication has been observed in the three main species, and in subtertian four successive generations have been obtained, but frequent subinoculations are necessary. The medium is delibrinated blood containing dextrose. Croscents have been produced in artificial cultures of P. falciparum after 10 days' incubation (Sinton). Some interesting facts have been observed in the morphology of the cultivated parasites; for instance, the number of merozoites formed during schizogony is considerably greater than in the blood-stream under natural conditions, whilst the parasitized cells show a tendency to agglomerate, a feature which does not take place in benign tertian cultures. P. gallimaceum has been grown in tissue-culture by F. Hawking (1944), and this method is applicable to other species such as P. lophurer.

Black (1946) has improved the technique of culture. Blood serum is obtained from 20–30 ml, of blood in a large test-tube containing 0-1 ml, of 50 per cent, glucose solution and stirred for five minutes till defibrination is complete. The serum is separated by centrifugation and placed in a flat-bottomed tube ½ in, in diameter to give a column of serum ½ 2 in, high. Red cells infected with P. falciparum are obtained from beneath the leucocyte layer after centrifugation. These are introduced into the bottom of the serum tube which is incubated at 37° C. Schizogony followed by invasion of new red cells is observed after 28 hours. At 78 hours forms resembling gametocytes appear, but after five days parasites are scanty. Subcultures into free scrum containing red blood corpuscles and glucose give results similar to the initial culture. By this method it is possible to test the effect of drugs in the scrum on the parasites. Cultures are made with a moderately heavy infection (100,000 parasites per c.mm.)

Exflagellation. —When malaria-infected blood is cooled outside the body the flagellated body derived from the microgametocyte is observed and represents a process which cannot occur in the circulating blood. This body, composed of colourless protoplasm and actively oscillating pigment granules, floats in the plasma. It first becomes circular and then the flagella (microgametes), six or more in number, with bulbous extremities, crupt from the periphery. For a

period the flagella lash and vibrate, agitating the plasma in which they lie, but eventually these delicate filaments break away from the parent body and swim with rapid movements (Fig. 220).

Sexual Forms.—The gametocytes of the four human species of malaria parasites differ in shape. In the benign tertian, quartan and ovale they are round or oval, but crescentic in the subtertian. The "crescent" exhibits no amoeboid

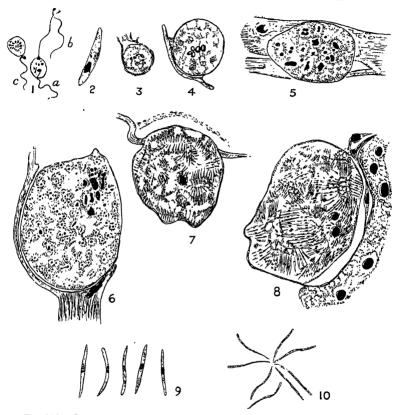


Fig. 220.—Stages in the development of Plasmodium falciparum in anopheles. × 2,000. (After Wenyon.)

(a) Enflagellation of male gametocyte of P. rivax; (b) free flagellum (male gamete); (c) fertilization
of female gamete.
 2. Ookinete.
 3. Encysted zygote in stomach wall.
 4, 5, 6. Oocysts showing
retaculated cytoplusm.
 7. Section of oocyst showing sporozoites forming outgrowths from cytoplasmic reticulum.
 8. Section of odcyst into mature sporozoites.
 9. Sporozoites from salivary
gland.
 10. Sporozoites of Plasmodium ocale.
 (After Shate.)

movement and contains needle-shaped pigment particles in its centre. In the male (microgametocyte) the protoplasm is hyaline with loosely arranged pigment; in the female (macrogametocyte) the protoplasm is faintly granular with the pigment arranged in a well-defined ring. In the subtertian, gametocytes are derived from corresponding stages within the red corpuscles agglomerated in the blood vessels of the internal viscera. It has been proved that injection of blood containing gametocytes into non-immune individuals does not produce malarial infection.

The flagella, or microgametes, are formed of a chromatic filament and a covering

of protoplasm, and after their cruption the remains of the parent cell consists of pigment granules and a small amount of residual protoplasm which are ingested

by wandering phagocytes (mainly large mononuclears).

Conditions favouring or retarding the cruption of microgametes. By exposing freshly-drawn malaria blood to air with slight admixture of water (as by breathing on the wet film) it is usually easy to produce and stain the flagellated body. In certain malarial bloods exflagellation takes place rapidly: in others it may be difficult (see p. 1077).

Granular spheres (female gametocytes) do not emit flagella, but become spherical and remain quiescent. The aim of the microgametes (flagella), when they have broken away, is to approach and endeavour to enter the granular spheres (female gametes). On the surface of the latter a minute papilla is seen to project, and at this point one of the microgametes enter, causing an instantaneous oscillation of its contents (Fig. 220, 1, C). Subsequently, although the sphere may be again energetically attacked, no second microgamete can effect entrance. This process (first observed by MacCallum in 1897) constitutes an act of fertilization.

DISCOVERY OF THE PRE-ERYTHROCYTIC CYCLE OF THE MALARIA PARASITES

In 1902 Schaudinn claimed to have observed the sporozoites from the salivary glands of the mosquito penetrate into a red blood corpusele and there develop into the ring form or trophozoite (sometimes called a schizozoite). For over thirty years Schaudinn's work remained unchallenged and formed the basis of every illustration in text-books, in spite of repeated attempts by other workers to confirm it. In 1924, Yorke and Mactic pointed out the main differences between therapeutic malaria conveyed by inoculation, and the naturally acquired mosquito-conveyed disease. The former is much more easily cured by quinine and has a much shorter incubation period. To explain these anomalies, James, in 1931, suggested that the sporozoites, on their entry into the human body, passed into the tissues where they underwent development before reaching the blood stream. This hypothesis received support when tissue-invading forms of plasmodiidæ of birds were demonstrated by Raffaele, Kikuth, Mudrow, James and Tate. The complete cycle of P. gallinaceum was worked out by Huff and Coulston (1944). In 1947 (as already related on p. 887) tissue forms were found in a bat and later by Garnham in monkeys infected with Hepatocystis kochi.

Fairley, in 1945, made the important observation that the infectivity of the blood after inoculation with sporozoites remained so for seven minutes up to half an hour. Thereafter, for several days negative results were obtained. In *P. falciparum* infections, subinoculations from the seventh day were positive; in *P. vivax* from the ninth day. This evidence could only be taken as suggesting that some tissue-cycle in the body was taking place.

In 1948 Shortt, Garnham and Malamos, working with $P.\ cynomolgi$, a simian parasite closely resembling $P.\ vivax$ of man, found in the liver of the monkey numerous large parasites measuring 25–30 μ in diameter and which resembled the tissue forms of bird malaria (cryptozoic schizonts). Soon after Shortt and Garnham, in collaboration with Covell and Shute, and by using large numbers of infected mosquitoes which were made to bite a volunteer, succeeded in demonstrating the tissue stages of $P.\ vivax$ in a piece of liver removed by biopsy. In $P.\ cynomolgi$ also pre-crythrocytic schizogony takes place in the cells of the liver. The earliest forms are seen on the fifth day after infection. They are spherical or ovoid bodies, about 10 μ across, containing 50 pieces of irregular chromatin. Maturation occurs on the eighth or ninth day, at which time a few vacuoles develop in the parasite and indentations of the periphery occur. Nuclear multiplication continues and nearly a thousand merozoites are formed. The mature schizont measures about 35 μ in diameter.

Persistence of the tissue cycle in the liver cells has also been demonstrated by Shortt and Garnham (1948). Schizonts were found $3\frac{1}{2}$ months after the original sporozoite infection and after a month's latency, when the parasites were absent from the peripheral blood. The cryptozoic schizonts of $P.\ vivax$ resemble those of $P.\ cynomolgi$ very closely. They exhibit vacuoles, indentations of the periphery, and nuclear multiplication resulting in the formation on the seventh day of a fully mature schizont with 800–1,000 merozoites. The size of the schizont is a little larger than that of $P.\ cynomolgi$ —about 42 μ in diameter.

P. falciparum.—The pre-erythrocytic development, with liberation of merozoites, may be completed in less than a hundred and thirty-five hours after mosquito transmission of P. falciparum (Shortt, Fairley, Covell, Shute and Garnham, 1949). Fourth-day forms of schizogony are oval, measuring 31 μ in the largest diameter and showing a tendency to produce lobose projections. They contain numerous nuclei measuring 1.5μ across. At first the liver cell is only slightly altered, and its nucleus is pushed to the periphery. The five-day schizonts measure 50 μ in their longest diameter. At this stage the production of lobes is marked and there is a tendency of the cytoplasm to break up into portions resembling eytomeres. The number of nuclei which are now smaller increases considerably and many are dividing. Six-day schizonts measure upwards of 60 μ and form a complicated system of lobes, so that they are highly irregular in shape (dumb-bell shaped). At this stage schizonts have reached maturity and are segmenting into merozoites, measuring 0.7μ in diameter. They are either ready to rupture, or are releasing merozoites into the surrounding sinusoids. In number there may be 40,000. The parasites are surrounded by a limiting membrane. In comparison with a similar stage of P. vivax the phase is of shorter duration, the mature schizont is much larger and many more cryptomerozoites are produced.

SUMMARY OF THE LIFE-CYCLE OF HUMAN MALARIA PARASITES

Malaria parasites belonging to the family Plasmodiidæ undergo four cycles of development:

- (I). The pre-crythrocytic development in the liver of the *sporozoite* derived from the salivary glands of the mosquito.
- (11). The exo-erythrocytic cycle with the development of exo-erythrocytic (cryptozoic) schizogony which takes place in the liver cells in the case of the human species of Plasmodium.
- (III). Asexual erythrocytic cycle by schizogony in the red blood corpuscles of the circulating blood.
- (IV). The sexual cycle commencing with the growth of gametocytes in the vertebrate host and continuing with sporogony in the stomach cells of the mosquito.

As the descriptions of the full life-cycle of malarial parasites have necessitated an extension of the nomenclature, it is necessary to define some of the terms which are now coming into general use.

Pre-crythrocytic schizogony.—This term refers to the development of the sporozoite during the incubation period. It may occupy one generation only, as in mammalian malaria, or several generations, as in the avian forms.

Exo-crythrocytic schizogony.—It is necessary that this term should be confined to stages seen in the post-patent period—when the parasites have reached the blood and, in the case of the human parasite, have entered the liver cells.

Tissue Phase.—As this term embraces both pre-erythrocytic and exo-erythrocytic schizogony, it should be used when the exact stage of the infection is unknown.

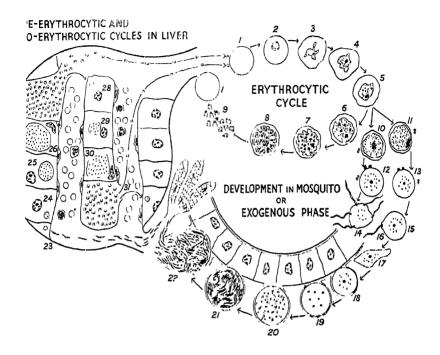


Fig. 221.—Schema of the complete life-cycle of mammalian malaria parasite based on Plasmodium vivax and P. cynomolgi. (After Shortt and Garnham.)

1, 1.	Normal red cells,
2, 3, 4, 5.	Red cells containing young parasites (trophozoftes),
6, 7, 8.	Erythrocytic schizogony,
9.	Liberation of crythrocytic merozoites into blood,
10, 11.	Development of male and female gametocytes in circulating blood.
12.	Mature male gametocyte extruding polar bodies,
13.	Matare female gametocyte extruding polar bodies.
14.	Exflagellation of male gametocyte producing male gametes (microgametes) in stomach of mosquito.
15.	Female gamete, or unacrogamete, being fertilized by male gamete to become a zygote.
16.	Male gamete or microgamete.
17.	Obkinete, or travelling vermicule, formed by clongation of zygote about to penetrate epithelial lining of mosquito's stomach.
18, 19, 20, 21.	Obeysts developing on outer wall of mosquito's stomach.
22.	Mature offeysts rupturing and liberating sporozoites which enter cultvary glands,
23.	Sporozoite from salivary gland of mosquito entering liver cell of man.
21, 25, 26.	Development of pre-crythrocytic schizont in liver cells.
27.	Pre-arythrocytic schizont liberating pre-crythrocytic merozoites (cryptomerozoites) which enter red cells, to commence the cryptomerozoites to repeat the development, or excessively schizogony.

Stages of exo-crythrocytic schizogony ending in a second generation of merozoitas (metacryptomerozoites). Rupture of exo-crythrocytic cryptozolc schizont of any later generation to maintain cryptozolc cycle in liver, or to produce relapse by restarting the crythrocytic cycle by metacryptomerozoites.—(P.H.M.-B. and W. Cooper). 31.

28, 29, 30.

 $\label{lem:process} Phanerozoite. \\ -- \text{Any exo-crythrocytic parasite except the pre-erythrocytic forms.}$

Cryptozoitc.—This term has been introduced to denote the first stages in the development of the sporozoite. Cryptozoites are the product of the first division of the sporozoite and are contained in a cryptozoic schizont.

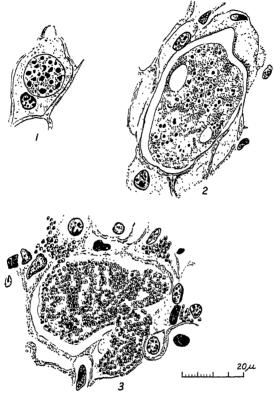


Fig. 222.—Pre-erythrocytic cycle of malaria parasites.

1.—Pre-crythrocytic (cryptozoic) schizont of Plusmodium cynomolgi in liver cell on 5th day, 2.—Pre-crythrocytic (cryptozoic) schizont of P. vivar on 7th day in liver cell showing form with two vacuoles, 3.—More advanced stage of pre-crythrocytic schizont of P. vivar showing formation and release of pre-crythrocytic merozoites (cryptomerozoites).

(After Shortt and Garnham, 1918, Trans. Roy. Soc. Trop. Med. & Hyg.)

Metacryptozoite.—After the first cryptozoic generation there are schizonts which produce metacryptozoites, and the term includes all pre-crythrocytic stages with the exception of cryptozoites.

Micromerozoite.—Certain exo-crythrocytic schizonts consist of many nuclei and little cytoplasm and these microschizonts produce large numbers of micromerozoites. In size and structure, they resemble the merozoites resulting from schizogony in red blood corpuscles and are destined to enter them.

Macromerozoite.—These are larger bodies than the micromerozoites and they are fewer in number. They do not invade red blood corpuscles, but enter tissue cells.

Schizonts.—The term schizont is properly applied to an intracellular asexual form in any stage, but in practice it is restricted so as to designate asexual forms other than ring forms. When chromatin has fully divided with formation of merozoites, the schizont is known as an adult schizont, sporulation form, segmentation form, or rosette.

TAND H. PRE-ERVTHROCYTIC AND ENO-ERVTHROCYTIC CYCLES (Fig. 221),—The pre-crythrocytic and exo-crythrocytic cycles of development can now be summarized. Inoculation of *sporozoites* by the infected mosquito is followed by the development of the pre-crythrocytic cycle in the cells of the liver, with production of pre-crythrocytic merozoites (cryptomerozoites).



Fig. 223.—Pre-erythrocytic schizont of P. falci parum in human liver, 6th day. (After Shortt, Fairley, and others.)

Some of these enter red blood corpuseles to produce a clinical attack of malaria by erythrocytic schizogony, but others enter normal liver cells and repeat the process (exo-erythrocytic schizogony) and thus produce the beginning of a relapse by the liberation of a second generation of merozoites (metacryptomerozoites). This repeats itself indefinitely, irrespective of whether the crythrocytic or blood cycle is present or is held in abeyance by anti-malarial treatment or, as appears probable, by naturally acquired immunity (Fig. 222).

III. ERYTHROCYTIC CYCLE. The cryptomerozoite enters an crythrocyte and growth then takes place at the expense of the red cell (crythrocytic or asexual schizogony). After two or three days, the single nucleus, by repeated division, multiplies into a number of daughter-nuclei. The parasite then produces a corresponding number of crythrocytic merozoites, a mass of residual protoplasm and characteristic pigment. By rupture of this cell, the merozoites escape into the plasma and attach themselves to other red blood corpuseles; the cycle is then repeated (asexual schizogony). When several generations of

¹ In P. vivar the merozoites enter retlemocytes; P. malaria enter effete crythrocytes, but P. falciparum enters any form of red cell.

merozoites have been produced, certain individuals become gamelocytes, or sexual cells (sporogony), which, when mature, are of the same size as the schizonts, but contain more pigment granules and a single nucleus.

1V. Sexual Cycle.—These cells are of two types, male and female (micro- and macrogametocytes), of which the latter has a dense and deeply-staining protoplasm. They are capable of further development only when taken up by a specific species of anopheles mosquito. In the male the nucleus divides and the daughter-nuclei proceed to the periphery of the cell to become the nuclei of the finaments endowed with motile powers (microgametes). In the meantime the female gametocyte (macrogametocyte), having shed its polar bodies, has become the macrogamete and is ready for fertilization by the microgamete. The impregnated macrogamete (or zygote) is capable of independent movement, clongates and, as an obkinete, bores its way through the lining epithelium of the

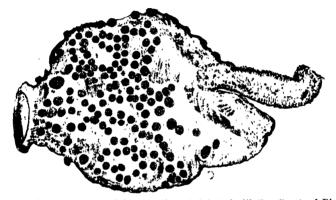


Fig. 224.—Stomach of Anopheles muculipennis infected with the oocysts of Plasmodium vivax.

mosquito's stomach, breaks up by meiosis, encysts between the epithelium and the limiting membrane and becomes an oöcyst (Fig. 224). The original nucleus of this cyst divides repeatedly, the protoplasm segments around the daughter-nuclei forming a spongioplasm. Eventually these nuclei arrange themselves on the surface of the protoplasm in which the sporozoites (about 15 μ in length) are formed, each nucleus acquiring an appropriate amount of cytoplasm. When fully filled with sporozoites the oöcyst bursts, setting them free. Some pass into the salivary glands of the mosquito, then travelling via the salivary duets they once more enter the blood when the mosquito proceeds to feed on its next victim, and are carried to the liver to recommence the pre-crythrocytic cycle. Not only are the sporozoites found in the salivary apparatus, but the whole body cavity becomes choked with them, and they may even penetrate the legs and antenne (Fig. 225).

The occyst also contains pigment granules, and one or more residual cytoplasmic bodies. The number of occysts present in the stomach of a single mosquito varies with the number of gametocytes in the blood. Sometimes only one or two occysts occur; sometimes ten to twenty; exceptionally there are large numbers.

The optimum conditions for development of malaria in anopheles are a mean temperature of 20-25° C. with a mean relative humidity of 60 per cent. or over. At a constant temperature of 15° C. P. vivax ceases to develop, but P. malariæ

continues to grow at 16·5° C.—At 20° C, the cycle in P, rivax occupies 16 days, in P, falciparum 22, and P, malaria 32–35.

Mosquitoes intected with *P. vivax* may be chilled; development of the parasites is merely temporarily arrested, but in *P. falciparum* the occysts shrivel if kept at freezing point for 48 hours. In some species of anopheles, although 50 or more occysts may be found in the stomach, full development does not proceed further. When once sporozoites have been developed the infected anopheles is capable of producing infection at extremely low temperatures and remains infective for three months.

In malaria man constitutes the *intermediate* (asexual cycle) and the mosquito the *definitive* host (sexual cycle).

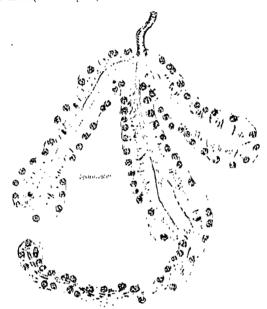


Fig. 225. Salivary gland of Anopheles magnificants containing sporozoites of Plasmodium falciparum compiled from serial sections. (After Wenyon.)

Differential characters of the oocysts of various species of malaria parasites. According to Shute the oocysts of the four species of human plasmodium exhibit differentiating characters in the arrangement and number of the pigment granules. In P. vivax the pigment is scattered without any definite pattern; the granules are line, yellowish-brown and exceed 70 in number. In P. ovale the pigment forms a definite pattern. It is coarser and darker in colour than in P. vivax, less so than in P. falciparum and P. malarie. The number of granules in an oocyst seldom exceeds 50. In P. falciparum the pigment forms a definite pattern, is jet black and very coarse. The number of granules in an oocyst rarely exceeds 20. In P. malarie the granules are also coarse and dark and the number of pigment granules less than 20 (Fig. 226).

Dissection of anopheles.—No particular difficulty should be encountered in recognizing malarial occysts, even under a low power of the microscope. They are spherical, refractile bodies which jut out beyond the stomach cells. With

a higher power ($\frac{1}{6}$ in. lens) characteristic black pigment can be discerned in their interior.

There are some misleading appearances, such as large body-cells ("pancreatic cells") and other objects, such as gregarine cysts and larval nematodes, which may occur in the anopheline stomach. Sporozoites may be recognized as fine refractile bodies in the cells of the salivary glands (Fig. 227).

Ross's black spores.—Sometimes of cysts may be encountered in which the cyst wall is completely filled with dark brown or black masses, which appear to represent degenerated cell contents which have undergone chitinization comparable to chitinized larval filariæ (Fig. 161, p. 744). Mayne claimed that these black spores are always associated with branches of the tracheal system of the mosquito. There is, however, no general agreement of their nature. Some regard them as representing an invasion by a fungus which preys upon the of cysts, but they are never encountered save in infected mosquitoes.

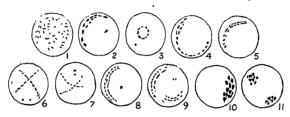


Fig. 226.—Diagrams representing typical arrangement of pigment granules in 3-4 day oöcysts. (After Shute.)

1, Benign tertian with golden-brown pigment. 2-5, Subtertian with black pigment. 6-9, Ovale tertian with dark brown pigment. 10-11, Quartan with coarse black pigment.

Infectivity of anopheles.—In endemic areas it is seldom that more than 4 per cent. of susceptible anopheles are found infected. (Christophers for A. culcifacies.) But when susceptible anopheles, such as A. culcifacies, gambiæ and maculipennis (clutus, labranchiæ and atroparvus) are fed on carriers rich in gametocytes, 90 or even 100 per cent. may become infected. Many factors in nature affect the infectivity of anophelines: e.g., the season, the number of infected malaria cases with gametocytes in their blood, and whether the insects favour human habitations or cattle sheds. In West and Central Africa 10 per cent. of A. gumbiæ and A. funestus are infected.

Shute has found that 100 per cent. of A. maculipennis atroparvus become infected with P. vivax when fed on carriers with gametocytes exceeding 4,000 per c.mm., but with P. falciparum rarely more than 50 per cent. become infected with a single feed. This has been confirmed by Boyd in Florida with A. quadrimaculatus and by Green in Malaya with A. maculatus.

In Bombay Bentley showed that 18 per cent. of A. stephensi were infected in August, but none in the dry season. Similar variations in the infection rate have been found in Holland in A. maculipennis (Swellengrebel). In America the infection rate of A. quadrimaculatus is 0.57 per cent., but in negro habitations it was as high as 4.9 per cent. (King). The fact that any particular species of anopheles can be infected in the laboratory does not by any means prove that it is capable of transmitting malaria under natural conditions, because this is a question of bionomics. Thus in Holland, England and Italy A. maculipennis vars messew and typicus play no part in malaria transmission, because they are zoophilic; they are easily infected in the laboratory, when they can be induced to bite man, and in North Roumania and Bessarabia they are important carriers,

domestic animals being scarce there. In England, however, A. m. typicus has not been found, only atroparcus and messew.

Sarcosporidia

Sarcosporidia are parasites which inhabit the muscular and connective tissues of vertebrates. They are clongated, sausage-shaped bodies with a cuticle within which are enclosed a number of falciform spores ("Rainey's corpuscles"). Sarcocystis produces a substance "sarcocystine" which is especially toxic for the rabbit. The cysts, which are visible to the naked eye, are commonly known as Rainey's or Miescher's tubes; they are frequently found in animals, but rarely in man in whom they have been recorded from the myocardium, larynx and arm muscles.

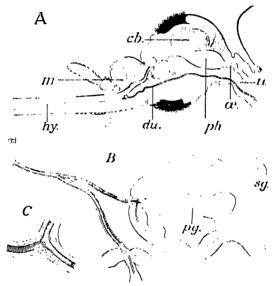


Fig. 227 .-- Dissection of head of mosquito.

A, Median section of head, showing du., the veneno salivary duct, with its invertion in hy,, the hypopharym; ch., cerebram: below this are the cerebellium and the pumping enlargement of ce, the cosphagus; m., nussele: n., nerve commessine. The other parts have been removed. B. The veneno-salivary duct, showing its bifurcation and the three glands on one of its branches; μα, poison gland; μα, marks the upper of the two salivary glands. C, The bifurcation of the duck with its nucleuted hypodermis.

The species in man is *Sarcocystis meischeriana* (8. lindemanni). There are several authentic cases on record. Lindemann (1868) found it in heart-muscle; Baraban and St. Remy (1894) in laryngeal muscles; Darling (1909) in the biceps of a negro; Manifold (1924) again in the myocardium.

TRYPANOSOMES

The structure of trypanosomes is uniform in type, though subject to variation in minor details. The body is slender, tapering to a fine point anteriorly, whilst the posterior may be pointed or blunt. In general shape it resembles a curved, flattened blade. The terms "flagellar" and "aflagellar" are sometimes used to designate the extremities in place of "anterior" and "posterior," which are employed strictly with reference to the mode of progression.

0

The nucleus is centrally situated; the kinetoplast is usually placed posterior to the nucleus, sometimes in close proximity. The axoneme, the axial filament of the flagellum, arises from a blepharoplast and passes forward along the margin of the undulating membrane; in some cases it may terminate with it at the anterior extremity, but more usually it is continued forward as the flagellum (Fig. 228). Those trypanosomes, in which the axoneme extends beyond the anterior end, are said to possess a free flagellum. Multiplication usually takes place by binary fission. The blepharoplast and kinetoplast divide first; this is followed by mitosis of the nucleus and formation of a new flagellum and membrane. The body then divides longitudinally in an antero-posterior direction. Trypanosomes occur as blood parasites in all vertebrates, so that many wild animals harbour them and different species are specific to particular hosts and, in the majority of cases, appear to be non-pathogenic.

Transmission.—With the exception of *T. equiperdum*, which passes from horse to horse during coitus, trypanosomes are transmitted by blood-sucking invertebrates, usually insects, but in fish and turtle by leeches. In *T. evansi* this transmission is mechanical and the blood-sucking fly, after feeding,

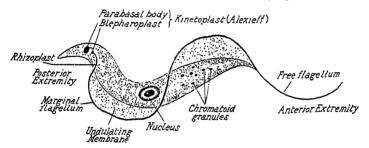


Fig. 228.—Schema of Trypanosoma. (After Dobell.)

within a short interval bites an uninfected host, in this manner inoculating directly those trypanosomes which adhere to the proboscis. In most cases, however, transmission is effected by a development cycle (cyclical development) in the fly, so that after an infective feed a definite intrinsic period is passed through before the fly is capable of conveying the disease. The infective stage is then known as a metacyclic trypanosome. Two main types of development are recognized:

(a) Anterior station.—Development commences in the stomach of the fly, spreading forward to the proboscis and salivary glands, or it may be solely confined to the proboscis.

(b) Posterior station.—Development commences in the stomach and passes backwards to the hindgut.

In the anterior station metacyclic trypanosomes are inoculated during the act of biting, whilst in the posterior station they escape in the faces of the insect and infect their host through the mucous membranes, as in T. cruzi.

Pathogenic trypanosomes of Africa are transmitted by species of the tsetse fly, Glossina, in which three types of development in the anterior station are known to occur. In the case of T. gambiense (Glossina palpalis, G. tachinoides), T. rhodesiense (G. morsitans and G. suymertoni) and T. brucei (G. morsitans), the ingested trypanosomes start to develop in the stomach, where long slender individuals are evolved, which in turn migrate forwards to the proventriculus, proboscis and salivary glands. There they are transformed into crithidial forms, which attach themselves to the gland cells and finally become metacyclic trypanosomes

resembling the short stumpy forms normally found in the blood. These are inoculated with the saliva during biting. The whole cycle normally occupies a period of about twenty days. In *T. congolense* there is a stomach development, but long slender trypanosomes pass forward to the proboseis —not to the salivary glands, where crithidial and metacyclic trypanosomes are formed. In *T. vivax* there is no stomach phase, but trypanosomes develop within the proboseis through the crithidial and metacyclic phases.

The posterior station method of development is exemplified by T, cruzi which is transmitted by reduviid bugs (Panstrongylus, Triatoma); development commences in the stomach and proceeds in the hindgut, where crithidial forms are produced and metacylic forms escape from the intestine in the faces.

In trypanosomes transmitted by the tsetse flies (Glossina) an important function is subserved by the peritrophic membrane, first elucidated by Hoare in the case of T. grayi. This is a soft cylindrical membrane extending from the proventriculus to the hindgut, where it is patent and is in reality a cylindrical tube suspended in the intestine. It is derived from an annular ridge or ring of gland cells in the proventriculus which secrete a viscous fluid which immediately solidifies as it is pushed progressively backwards. The ingested blood does not therefore come into contact with the gut wall, but osmosis takes place through the peritrophic membrane and the trypanosomes cannot penetrate it. Up to the fourth day the trypanosomes are actually within the lumen of the peritrophic membrane; they then migrate and escape through the open posterior end of this membrane and proceed to pass forward outside it to the proventriculus. They thus find themselves in a cul de sac and penetrate the membrane at the point of least resistance where it is still fluid. They then pass to the esophagus and proboseis, to the end of the hypopharynx, and double back again to the salivary glands. There they become crithidia, attaching themselves to the salivary duets for two to five days, before becoming metacyclic trypanosomes. The whole cycle occupies some twenty days. The fly is not infective until this stage is reached, but thereafter remains so for life (about eight months).

Infectivity of *T. gambiense* for *Glossina* is slight—less than 10 per cent, under experimental conditions; whilst in nature less than 1 per cent, are found infected. Strains of *T. gambiense* vary in infectivity and this property appears to become lost in longstanding infections. In laboratory strains long absence from the natural vector is a factor. Polymorphism is also lost; only long slender forms may be encountered.

Mechanical transmission. T. gambiense can survive in the probose of Glossina for varying periods and can be injected mechanically. Further, it has been shown in Nyasaland that Musca spectandra, feeding on exuded blood, can ingest trypanosomes and pass them out via the faces into a brasions of the skin.

Cultivation.—Trypanosomes can be cultivated on certain blood-media; those of cold-blooded vertebrates and birds, as well as non-pathogenic species. T. lewisi, T. theileri, and T. melaphagium are easily cultivated in N.N.N. medium or its modifications, but pathogenic species T. gambiense, T. trockeiense, T. brucci, T. comgoleuse, and T. rivax cannot be maintained in these media, but growin Razgha's medium, provided these strains have not lost their transmissibility by the tsetse. T. cruzi resembles the non-pathogenic species in its adaptability to artificial culture. As a general rule, in culture, trypanosomes tend to develop as in the invertebrate host, crithidial, and usually metacyclic, forms being produced.

Trypanosoma gambiense (Dutton, 1902)

This trypanosome does not usually occur in the blood of man in any great numbers. Sometimes it is more readily revealed by gland or sternal puncture, or in the cerebro-spinal fluid. It varies greatly in length and breadth during different stages, as a general rule from 13–39 μ in length. The nucleus is central, the kinetoplast small and terminal, the undulating membrane well developed. Binary fission takes place in the blood, cerebro-spinal fluid, brain, kidney and, in the later stages, in scrous fluids. Polymorphism in the blood is a characteristic feature. Three types are recognized: short stumpy forms without a free flagellum, long slender forms with free flagellum, and intermediate types. Posterior nucleated forms are now known to be developed in experimental infections in laboratory animals, as in T. rhodesiense, so that this feature is no longer recognized as peculiar to that species. The parasite occurs, not only in the blood, but in lymphatic glands, cerebro-spinal fluid, and the substance of solid organs, especially the brain. Most laboratory animals can be infected, but haboons (Cynocephalus) and the sooty mangabey monkey (Cercocebus fuliginosus) are refractory.

T. nigeriense, formerly thought to be a different species, is now recognized as a variant.

Reservoir hosts.—In the laboratory most African antelopes have been experimentally infected by the bite of the tsetse (Glossina palpalis and G. tachinoides), but under natural conditions this association probably does not hold good. The swamp-dwelling Speke's antelope, or situtunga (Limnotragus spekei), has proved to be an efficient reservoir and T. gambiense can survive at least two years in its blood.

Speke's (*L. spekei*) is a handsome antelope, standing 36 in. at the withers. The buck possesses fine spiral horns. In ground colour it is uniform greyish-brown, and the head is adorned with white ocular and check spots with white chin. It is a very shy species, living in dense, impenetrable papyrus swamps, and so is seldom seen or shot by Europeans. The hoofs are long and widely splayed, but when it lives in dry land they become shortened and modified.

The rôle of native pigs in the Congo as a reservoir, though suspected, has not been established. *T. gambiense* is essentially a human trypanosome so that man himself forms the chief reservoir.

Trypanosoma rhodesiense (Stephens and Fantham, 1910) (Fig. 229, 2)

This is indistinguishable in human blood from T. gambiense, the same three types being recognizable. Until recently, it was thought that the production of posterior-nucleated forms in laboratory animals, especially the rat, was distinctive, but this is not so. In this host a change occurs in the nucleus, which assumes a position close to the kinetoplast or actually posterior to it. The proportion of posterior nucleated forms which are shorter than normal may be 50 per cent. in some laboratory animals. (Fig. 18, p. 134.) It has also been demonstrated that certain arsenical preparations, administered to animals infected with trypanosomes which have lost this trait, caused a reversion to type. Goats and horses infected with T. rhodesiense develop interstitial keratitis of the eyes, and the organism can be demonstrated in interstitial tissues outside the blood-vessels. Some authorities still regard T. rhodesiense as a human strain of T. brucei, with which it is morphologically identical. Others regard it as T. gambiense, of a more virulent race, transmitted by a different species of Glossina—G. morsitans—but this view has not gained much support.

Geographical distribution.—I. rhodesiense is confined to North Nyasaland, North-East Rhodesia, Portuguese East Africa and Southern Sudan. Generally speaking its pathogenicity is greater than that of T. gambiense; it is more resistant to treatment and more virulent to laboratory animals.

Development in Glossina proceeds in G. morsitans, in the same manner as already described. In Tanganyika (Mwanza) it takes place in G. swynnertoni.

Reservoir hosts. It is becoming clear that a large number of antelopes can harbour T, thodesiense under natural conditions. Fairbairn and Burtt transmitted this trypanosome to humans by employing a strain which had been passed through various animals by G, more than for G years. Three main species of antelope are important.

Waterbuck (Kobus ellipsiprymnus). This handsome and familiar antelope ranges from the Limpopo River to Tanganyika, Kenya, and as far north as Somaliland; in the west it is replaced by an allied species (K. defassa). It has a white ribbon on the rump extending down the thighs on both sides, and is provided with a tough hide and coarse hair. It favours large swampy plains overgrown with reeds and papyrus.

Reedbuck (Redunca arundinacea). This animal stands 36 in. at the withers and

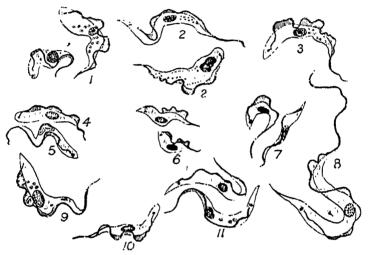


Fig. 229. Various trypanosomes of man and animals. × 1,300. (After Wenyon.)

T. gumbiense; 2, T. rhodesiense (brucci); 3, T. cransi; 4 and 5, T. uniforme, T. vicar; 6, T. congolense;
 T. t. cruzi; 8, T. theileri; 2, T. equinum; 10, T. equiperdum; 11, T. tewisi.

is greyish-fawn. There is a thick, bushy tail reaching half-way to the hocks. The female is hornless, but otherwise resembles the male, which possesses short curved horns. There are five varieties, and reedbucks are plentiful round Lake Nyasa, ranging north to Mozambique and west to Angola. It is easily approached and is remarkably unsuspicious. Its gallop is slow and irregular. A herd when alarmed utters shrill screams, kicks up the heels and tosses the tail.

The Duikerbok (*Cephalopus grimmi*). This is widely distributed in Central Africa. It is 23 in, in height, and pale greenish-brown. Small horns, up to 5 ins. long, are present in the male. The name duiker, or diver, comes from its habit of ducking or diving quickly into bushes when alarmed.

Trypanosoma cruzi (Chagas, 1909)

Synonyms.—Schizotrypanum cruzi; T. escomeli.

This trypanosome was first found by Chagas in the bug, Panstrongylus, and subsequently in man. It occurs in the blood of man in Brazil, Venezuela, North Argentina and in Central America (Panama, Guatemala) and is the cause

of Chagas' disease. Trypanosomes, indistinguishable from T. cruzi, have been found by Malamos (1935) in the blood of Macaca cynomolgus from Java, and again by Fulton and Harrison (1946) in M. mulatta from India. This suggests the possibility that this disease has a much more extended distribution than hitherto supposed, but in the instances cited infection from accidental causes cannot be excluded.

In its life-history (Fig. 230) it differs materially from others by its manner of development. Some forms are broad, others narrow, but it invariably assumes a C-shaped attitude in the peripheral blood. Average individuals measure 20 μ in length. The posterior end is pointed and the kinetoplast is large. (Fig. 229, 7.)

Certain trypanosomes leave the bloodstream and invade muscles, especially the myocardium, or the cells of the brain or other organs, and there undergo a series of binary fissions during which they assume a leishmanial appearance. Multiplication is so rapid that soon large accumulations are formed in the tissues. Later, the leishmanial forms elongate and become crithidia; later still they become transformed into trypanosomes, which make their way through the tissues and enter the bloodstream.

Life history.—Trypanosomes are abstracted from human blood by a reduviid bug, Panstrongylus (Triatoma) megistus, in which they undergo a complicated development. This can take place either in larval, nymphal or adult stage of the insect. The trypanosomes pass into the midgut, become transformed into crithidia and as such continue to multiply rapidly. They enter the rectum, where metacyclic or infective trypanosomes appear and then pass out in the fæces of the bug. (Fig. 230, 1.) Inoculation of the parasite into man takes place by contamination of mucous membranes with fæces or by rubbing fæcal matter into the wound originally made by the bug. Incidence of infection of bugs may be very high. In Brazil 41 per cent. of P. megistus; in Chile 50 per cent. of Triatoma infestans and T. spinolai and 37.5 per cent. of T. protracta infected in California. (Infection of monkeys with T. cruzi isolated from triatomid bugs in U.S.A. has been accomplished by Wood.)

These bugs live in cracks and holes in the thatch of primitive houses. Their bite is painless and usually occurs at the junction of mucous and cutaneous surfaces as in the lip. Hence the name of "kissing bug." They bite at night, and retire to their hiding places before daylight.

Under experimental conditions, T. cruzi can be inoculated into rats, mice, rabbits, guinea-pigs and monkeys, and can pass through the mucous membrane of the mouth or conjunctiva. T. cruzi can be readily cultivated in liquid medium consisting of a solution of peptone, glucose and sodium chloride with coagulated rabbit blood corpuscles. Hawking (1947) has grown the parasite in tissue culture, using a suspension of trypanosomes from the blood of an infected mouse added to a culture of rat embryo. During the first two days great numbers of trypanosomes are present in the culture fluid, but after six days considerable numbers of intracellular parasites in all stages of development are seen in cardiac muscle, in macrophages and in the reticulo-endothelium.

A large number of reduviid bugs have been found capable of transmitting T.cruzi. In Mexico no less than fifteen species have been found naturally infected. Amongst these are: Triatoma~phyllosoma, T.~pallidipennis, T.~rubida, T.~barberi, T.~dimidiata, T.~picturata, T.~longipennis, Rhodnius prolixus and Dypetalogaster maximus. Other species in Brazil are <math>Panstrongylus~megistus, in N. Argentine, Chile, and Uruguay, T. infestans, T. sordida, T. vilticeps, T. dimidiata var. maculipennis; in Venezuela, Rhodnius prolixus and Eratyrus cuspidatus. Other species are Eutrialomu maculata, E. nigromaculata, E. osvaldoi, E. patagonica, E. rubrovaria, E. sordida, Panstrongylus~geniculatus, Psammolestes~arthuri,

P. coreodes, Rhodnius brumpti, R. domesticus, R. pullescens, R. pictipes, R. protixus, Paraiochamus carroca, Triatoma brasiliensis, T. carrioni, T. capitis, T. chagasi, P. cruzi, T. genwulata, T. hegneri, T. maculipennis, T. platensis, T. protracta, T. rubida, T. rosenbuschi, T. sanguisuga, T. spinolai.

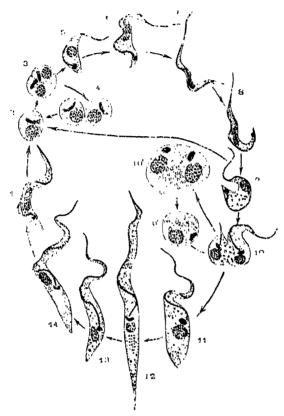


Fig. 230. Evolutionary cycle of Trypanosoma cruzi: 2-9 in man or other vertebrate; 9-14 in Panstrongylus, Triatoma or Cimex. × 1,500. (After Brumpt.)

Melacyclic trypanosome infecting vertebrate; 2, 3, 4, achizegony in organa; 5, 9, transformation
of adult trypanosome (9); 10, crithidial form about to divide in small intestine; 104, leishmania
forms frequent in the proventriculus; 11, 11, progressive transformation of crithidia forms into
metacyclic trypanosomes (1) in bludgat.

A species common in California (Triatoma protracta), extending as far north as Salt Lake City, harbours a trypanosome resembling T. cruzi, though the human disease is unknown there, whilst, under experimental conditions, other members of the Triatoma genus in the United States can be easily infected, as well as cosmopolitan species, T. rubrofasciata and T. dimidiata (Ecuador). In Arizona it is Eutriatoma uhleri; in New Mexico E. protracta woodi; and in Texas T. gerstækeri. It is probable that all species of Panstrongylus and Triatoma are susceptible to infection. Under laboratory conditions Brumpt has observed development in bugs, Cimex hemiptera (ratindatus), C. lectularius, C. boucti, C. hirudinis, and in ticks, Ornithodorus moubata and O. savignyi.

Reservoir hosts.—The multiplicity of the vicarious hosts of *T. cruzi* certainly indicates that the organism would spread to many countries, if other conditions remained favourable. These reduviid bugs are so easily infected that 100 per cent. become so at all stages of their existence and, moreover, remain so for the whole of their lives. The method of identifying *T. cruzi* in reduviid bugs is known as xenodiagnosis.

T. cruzi has been found in cats and dogs, but under natural conditions it occurs mainly in several species of armadillo (Edentata), Euphractus vellerosus—the long-haired armadillo, Dasypus novemcinctus—the Peba armadillo, D. novemcinctus fenestratus, Euphractus sexcinctus—the six-banded armadillo, Cabassous unicinctus—the broad-banded armadillo, Chælophactus vellerosus, Zoedypus pichiy—and the little armadillo, Tolypeutes tricinctus matacus.

Probably $T.\ cruzi$ is naturally a parasite of armadillos, but occasionally becomes inoculated into man.

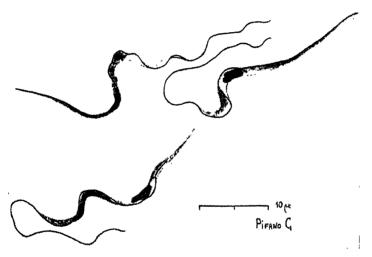


Fig. 231.—Trypanosoma rangeli. Forms in culture from the peripheral blood. (After Pifano and Mayer.)

Other mammals include:

Canida. Pseudalopex culpaus—Colpeo Fox; Dueyon gracilis gracilis. Chiroptera. Histiotus læphotis, H. montanus, Myotis nigricans, M. dinellii.

M. levis.

Carollia perspicillata, Antibeus jamaicensis, Desmodus rotundus

marinus (Panama). Dirias albiventa.

Talarida macrotis.

Glossophaga. Soricina leachi, Carollia perspicillata azteca, Phyllostomus hastatus, Uroderma bilobatum (Panama).

Mustelidæ. Grison cuja huronax—Grison; Tayra barbara—Tayra.

Agoutis. Octadon degus.

Marsupialia. Didelphis azara, D. marsupialis mesamericana (California).

Lutralina crassicauda paranalis, Marmosa cinerea, Metachirus nudicaudatus.

Anteaters. Pamandua tetradactyli kriegi.

Sciuridae. Sciurus argentinus Argentine squirrel.

Monkeus. Saimiri sciurcus.

Rodents. Neotoma fuscipes Woodrat (California).

N. albigula (New Mexico, Arizona).

T. cruzi has been found by Malamos in four out of ten monkeys (Macaca syruchta mordux) imported from Java.

Backhouse and Bollinger have shown that the Australian phalanger or possum

Trichosurus vulpecula—is very susceptible.

The most important reservoir is the armadillo, which is widely distributed throughout America and is found in burrows in the vicinity of human habitations where the bugs (Panstrongylus and Triatoma) abound. The long-tailed species (Dasypus novemeinetus) is the commonest, and abounds in Guatemala up to 5,000 feet. The "peludo," Euphractus sexcinctus, a much smaller species 18 in, in length, is specially common in Brazil.

Trypanosoma rangeli (Tejera, 1920)

This species occurs in Guatemala, Uruguay, Colombia and Venezuela,

It was first found in *Rhodnius prolicus* and subsequently sparingly in man, in the same districts where *T. cruzi* occurs. Human infections have been described by Medina, Pifano and Mayer, especially in children. According to Hernandez Paredes (1949) the illness in man is characterized by bouts of fever and sweats resembling exanthemic typhus. Pifano has recorded 41 human cases in Yaracuy (Venezuela) of which 31 had a double infection with *T. cruzi*. This trypanosome is readily cultured in citrated blood and glucose agar with defibrinated rabbit blood in Locke's solution. Positive inoculation in rabbits and white mice can be obtained.

The parasite is pear-shaped with a minute blepharoplast and much more elongated ($50\,\mu$) than T. cruzi (Fig. 231). Oval and crithidial forms are found in the intestinal contents of the bug and the latter forms in its faces. The presence of this parasite is best proved by xenodiagnosis and by blood culture on N.N.N. medium. Its pathogenicity is at present uncertain.

Trypanosoma ariarii N. sp. Groot, Renjifo and Uribe (1950). This is a long slender trypanosome, closely resembling T, rangeli and measuring 31 μ . The body is markedly undulant, with two curves on one side and one to three on the other. Both extremities are thin and attenuated so that it is difficult to define where the anterior extremity of the body ends, and where the free flagellum begins. The posterior portion becomes progressively thinner and ends in a sharp, sometimes curved, point.

The nucleus situated in the anterior part is granular, whilst the kinetoplast is small, rounded and 0.7 μ in diameter, whence the flagellum arises. The undulating membrane is wide, sinuous and well-developed. Rhodnius profixus is readily infected; some forty days after blood meal non-flagellated and flagellated stages can be demonstrated in the gut. From blood culture this trypanosome grows easily in Geiman solid medium at 28° C.

T. ariarii has been inoculated into baby white mice younger than six days, also in young opossums (D. paraguagensis), a monkey (M. mullata) and into human volunteers. Two of these remained in good health, though trypanosomes were demonstrated by blood culture between the thirteenth and tifteenth month after inoculation. The organism was found once only in a thick blood film. The area where this species is found is on the river Ariari in Colombia 20 min. N. of the Equator at 1,300 feet altitude.

From 183 of the inhabitants examined by blood culture 67 showed these trypanosomes. One dog and a monkey—Cebus fatuellus—were found naturally infected.

Trypanosoma lewisi (Kent, 1879)

This is a common parasite of the rat and is present in considerable numbers in the bloodstream (Fig. 229, 11) at the height of the infection. It has once been recorded from man, in a Sikh child in Malaya (P. D. Johnson, 1933). The trypanosomes were present in large numbers in the peripheral blood for five days. It is, however, non-pathogenic to the rat. Individual trypanosomes vary considerably in size and appearance during the muliplication phase, but in the chronic stage average about $24~\mu$. The nucleus is situated at a point slightly anterior to the centre of the body.

T. lemisi develops in Ceratophyllus fasciatus, Xenopsylla cheopis, and other fleas. Trypanosomes enter the epithelial cells of the stomach, where they become spherical and grow. The nucleus divides repeatedly, and young trypanosomes are formed by multiple division. These pass into the hindgut, and after two days become crithidia. Eventually they escape as small metacyclic trypanosomes in the exercta. They are then ingested by the rat, which either licks up the fleas faces or devours the insect. Trypanosomes appear in the bloodstream after an incubation period of six days.

LEISHMANIA

The parasites of this genus are found in man in kala-azar, oriental sore and the South American disease—espundia. The leishmania of kala-azar is L. donorani in the Old World. In Brazilthis parasite has been provisionally named L. chagasi, though its validity is doubtful. The organism of Mediterranean kala-azar, which is mainly confined to children, has been called L. infantum.

Cutaneous leishmaniasis in the Old World is caused by *L. tropica*, while the muco-cutaneous disease of South America is due to *L. brasiliensis*. Visceral leishmaniasis in dogs is attributed to *L. canina*. All these parasites are morphologically identical and the claim that they can be differentiated by serological methods has not been substantiated. Possibly, differences in pathogenicity after artificial inoculation of susceptible animals, probably the hamster, may be forthcoming.

Under natural conditions, infection of animals with the human leishmania are exceptional, though cutaneous leishmaniasis has been found in gerbilles (Middle Asia), cats, dogs, Syrian bears and horses. The Leishman-Donovan (L.D.) body is a small, round, oval, or eigar-shaped body from 1–3 or 4 μ in diameter. It consists of a minute mass of cytoplasm enclosed within a delicate membrane. Within is a nucleus and a kinetoplast. A rhizoplast is sometimes seen—a rod-shaped body representing the axoneme of the future flagellum, which is produced on artificial cultures and also within the gut of those sandflies (Phlebotomus) which serve as intermediary insect hosts for leishmania. In the visceral infection—kala-azar the parasites (L.l.) bodies) affect the reticulo-endothelium and are found, therefore, in endothelial cells, macrophages and plasmocytes, chiefly in the spleen, bone marrow and liver; in the skin, subdermal tissues and lymphatics in oriental sore (L. tropica), and in the skin and mucosa in espundia (L. brasiliensis). In zoological terms the L.D. body is classified as a leptomonad flagellate as is shown by its development in culture on artificial media.

Method of culture.—The development of Leishmania in Phlebotomus follows upon the same general lines as that of insect flagellates of the genus Leptomonas. In the tissues of man, L.D. bodies multiply by binary fission and, as originally shown by Rogers, they develop in culture media into leptomonad forms resembling the flagellates of the dog-flea (C. canis.) (Fig. 232).

Fully developed leptomonad flagellates are 14–20 μ in length by 2 μ in breadth, and the flag flum measures 16–24 μ . They progress actively with the flagellum in front, and in cultures exhibit a tendency to agglomerate in clusters, or rosettes, with their flagella centrally directed.

The culture medium originally employed by Rogers consisted of spleen pulp added to slightly acidified citrate of soda solution, but N.N.N. medium is better. A small quantity of infected material from kala-azar, or blood from a vein, or serum derived from the base of an oriental sore is added to the water of condensation in one or more of the tubes, which are then incubated at 22–25° C, and in 2-3 days flagellates appear in the fluid. It is essential that bacterial contamination should be excluded.

Life-history in the sandfly. Ever since the finding of leptomonad flagellates in the sandfly (*Phlebotomus*) by Wenyon (1912) and the production of

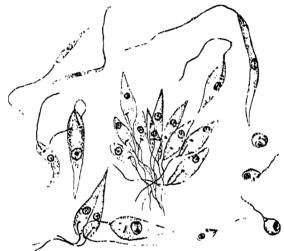


Fig. 232. Developmental forms of $Leishmania\ donovani$ from the leishman body to the crithidial stage, and clumping of the flagellated organisms. $\sim 2,000.$ (After Wenyon.)

typical oriental sores by the inoculation of crushed-up P. papatasii by Sergent and his co-workers (1921), attention has been directed to the genus Phlebotomus.

The peculiar topographical distribution of kala-azar in India led Sinton (1922) to suggest that *Phlebolomus argentipes* might possibly be the insect intermediary. In more recent years intensive work by Christophers, Shortt, Knowles, Napier, Barraud, Lloyd and Smith clearly demonstrated that rapid development of leptomonad forms of *L. donorani* takes place in *P. argentipes* fed on the blood of kala-azar patients in India. The whole midgut becomes infected and the flagellates then pass to the pharynx and to the buccal cavity forming a block (Fig. 21, p. 147). The distribution of this species of Phlebotomus in India corresponds with that of kala-azar. In other endemic areas other species are involved: in China, *P. chinensis*, and *P. sergenti*, var. mongolensis; in the Sudan, *P. langeroni*, var. orientalis; in Brazil, *P. intermedius*; in the Mediterranean, *P. major* and *P. perniciosus*, and, possibly *P. perfillewi*.

In India, P. argentipes readily infects itself by feeding on human cases when the organisms occur in sufficient numbers in the bloodstream. In the Mediterranean area the parasites are so scanty in the blood that the number of sandflies which become infected in this manner is negligible, though they commonly do so by feeding on dogs. Thus, in the Mediterranean, man is negligible as a reservoir compared with the dog. There is therefore a profound difference between the epidemiological character of Indian and Mediterranean kala-azar.

Difficulties were at first encountered by workers with sandflies, mainly on account of their delicacy and the difficulty of keeping them alive longer than five days after feeding. Then Shortt and his co-workers (1931) succeeded in transmitting L. donovani to hamsters (Cricetulus griseus) by the bite of infected Phlebotomus argentipes, but Swaminath, Shortt and Anderson (1942), by keeping these sandflies alive for two weeks after feeding on kala-azar blood, succeeded in conveying this disease to five out of an equal number of human volunteers. The sandflies were kept in an atmosphere of 28° C. and, after the original infecting feed on a kala-azar case, were fed on fruit juices in place of blood.

The cycle of development can be divided into two stages—after the first and second blood meals. First, the parasites enlarge and undergo binary fission; the flagellate leptomonads form on the second day; on the third they become elongated and active in the midgut, whilst short forms remain attached to the gut wall. On the fourth day they occur in masses near the proventriculus ("blocked" sandfly) and the fly is ready to lay eggs when ready for the second blood meal. Flagellates then move forward to the pharynx until they reach the proboscis. Transmission now takes place so that, when the sandfly next attempts to feed, the flagellates are dislodged from the buccal cavity and inoculated into the site of the bite.

Susceptible animals. Dog.—In recent years conviction has been growing that the dog is the principal reservoir of the disease for man in the Mediterranean area. Adder stressed the importance of house as well as street dogs in Canea, Crete. In Marseilles, Giraud and Bergier showed that the majority of cases are derived from suburban residences where canine kala-azar is frequent. In Algeria Sergent stated that the disease is transmitted by Phlebotomus perniciosus from dog to dog and from dog to man. Hoeppli in China found that P. chinensis is readily infected from local dogs, and that this animal must be considered an important reservoir in that country. This was confirmed by Feng and Lee in Peking and by Andrews in Mukden (Manchuria).

Throughout the endemic centre of the Mediterranean area the disease is far commoner in dogs than in man; e.g. in Malta out of a population of about 15,000 dogs 10-12 per cent. are infected, whilst out of a population of 250,000 human beings about 90 cases occur annually. It is therefore not surprising that there are endemic centres, where dogs are infected in considerable numbers, and where there are relatively few human cases, as in Morocco and Marseilles.

In Brazil, Chagas and his colleagues, failing to find leishmaniasis in wild animals, succeeded in doing so in domestic dogs and cats. In Malta, native dogs are found infected, especially during the summer. The majority are sick and emaciated. Seborrhoa and depilation are most marked outward signs of infection, being due to parasite-laden histocytes around the hair follicles. Infected cells are found distributed uniformly in the dermis and throughout the unbroken skin of the entire body of dogs, so much so that any bloodsucking arthropod is bound to ingest infected cells from the skin juice in the act of feeding. This explains the high infection rate of *P. perniciosus* and *P. major* when fed on infected dogs.

In Sicily and in Malta, Adler and Theodor found that both infantile and camine leishmania are transmitted by *Phlebotomus perniciosus*, and these insects can be infected by feeding them on dogs suffering from kala-azar. The aldehyde test is not so reliable as a means of diagnosis as in man. The rate of infection of dogs is: Algiers 7·1 per cent.; Tunis 1·8 per cent.; Lisbon 3·7 per cent.;

Malta 10 per ec.t.; Rome 16 per cent.; Messina 81 per cent.; Canea (Crete) 20 per cent.; Island of Hydra 17 per cent.

Other mammals.—In Morocco the Barbary ground squirrel (Xerus getulus) has been found naturally infected. In Brazil the Texas ground-squirrel (Citellus tredecimlineatus) has been found susceptible. The Chinese sand-hamster (Cricctulus griscus), susceptible to artificial infection, is a small species, 12 cm. in length and 30 grm. in weight. It has a range extending from Peking into Chinese Mongolia. Greyish-brown with median dorsal stripe, it has a short stumpy tail, lives in deep burrows, frequenting cornfields and destroying grain. The hamster of Syria, Palestine, Greece (Cricctus auratus) and the Macedonian

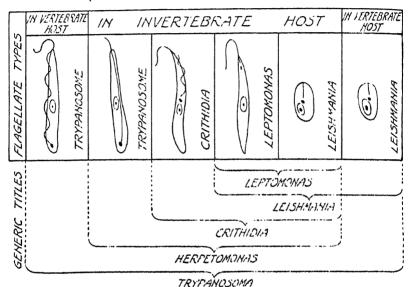


Fig. 233.—Diagram illustrating relationships of various genera of blood and tissue flagellates and the morphology of the various developmental forms and species.

(After Wenyon.)

spermophile (Citellus citellus), the European souslik, and other species of hamster (C. accedula and Cricctus cricctus) are very susceptible. In China, the mole rat (Myospalax fontanicri), the ground squirrel (Citellus dauricus); in Palestine, the field mouse, Guenther's vole (Microtus guenther'); in Sudan, the gerbille (Gerbillus pygargus) and the white-rumped gerbille (Jaculus gordoni); in Japan, a striped squirrel can be infected. Fulton and Niven have proved that the cotton rat (Sigmodon hispidus) is susceptible. Bolliger and Backhouse found that it Australian opossums (Trichosurus vulpecula and Pscudocheirus laviginosus), various eye lesions, conjunctivitis, interstitial keratitis and cutamets are produced. American marsupials (Didelphis marsupialis and Metachirus radicaudatus) are susceptible.

Transmission of L. tropica also takes place through phlebotomus, and follows the same method of development as L. donovani. The infective forms of leishmania are inoculated by the bite of the sandfly, and the resulting sores have been experimentally reproduced by Wenyon in Iraq, the Sergents in Algiers, by Adler

¹ Guinea-pig leishmaniasis was discovered by Median (1946) in S. Brazil and the parasite is L. cariettii (Muniz and Median, 1948). Primarily a entaneous infection, it spreads through the body via the tymphates.

and Theodor in Jerusalem, by the method of inoculating crushed infected sandflies or by feeding sandflies originally infected by ingestion of cultures. The species concerned in N. Africa and E. Mediterranean are P. papatasii and P. sergenti; in Iraq, India and Persia, P. sergenti; in Central Asia, P. caucasicus. In Brazil, N. Argentine and Paraguay, L. braziliensis is transmitted by P. intermedius.

Nomenclature of hæmoflagellates.—Four types of flagellates are recognized:-Leishmania, Leptomonas, Crithidia, and Trypanosoma. Certain flagellates have leishmanial and leptomonad stages only. When confined to the intestinal tract of insects they are referred to the genus Leptomonas: in insects as well as vertebrates to the genus Leishmania. Others again pass through leishmanial and crithidial stages, are confined to insects, and are classified as typifying the genus Crithidia (Fig. 233). Others again exhibit leishmanial, crithidial and trypanosomal stages. When found in insects alone they constitute the genus Herpetomonas, but if part of the life history is passed partly in insects, and partly in vertebrates, the parasite is then known as Trypanosoma.

TOXOPLASMA (Nicolle and Manceaux, 1908)

Toxoplasma is an intracellular protozoan, of which the type is *Toxoplasma gondii*, first described (1908) by Nicolle and Manceux in a N. African rodent, the gondi (*Ctenodactylus gundi*). Almost simultaneously, Splendore described a similar organism in rubbits in Brazil. The organism, as described by Sabin and Cllisky in guinea-pigs, was found within living cells, not only monogeres, but also every type of paren-chymal cell, and infection could be produced experimentally by intravenous, intranasal and other routes.

chymal cell, and infection could be produced experimentally by intravenous, intransast and other routes. The organism is clongated, with a curved or crescent form, 4-6 µ in length by 2-3 µ in breadth. It is pointed at each end. Reproduction is by longitudinal division. Its zoological status is doubtful. Cases have been reported from America, Czechoslovakia, Holland, Australia, and Italy. The first case in Hingland has been described by Jucoby and Sagoriu (1948).

Human toxoplasmosis was first identified in America in a case of infantile encephalomyelitis by Wolf, towen and Paige (1930). The parasites were found with ease in sections of the nervous system, and the protozon were transmitted to laboratory animals. Subsequently, some six other toxoplasma infections have been reported in infants. It has now also been recognized as a cause of mild encephalutis in older children. Chorio-retaintis is of diagnostic importance, and a full account of the ophthalmoscopic range of variations of the lesions was recorded by Koch (1943). The toxoplasma infection, which takes place in cetal life, evolus focal edgem and necross of the retam and adiacent chored. This is succeeded by a total life, excites focal celema and necrosis of the retina and adjacent choroid. This is succeeded by a granulomatous reaction. The protozoan has been identified in these lesions, but rarely in the choroid. Neutralization tests in rabbits with selected human sera suggest that toxoplasmosis may be more wide-Neutrinization tests in rainits with selected lumina sera suggest that toxoplasmoss may be more wheespread in N. America than generally supposed. Apparently in the mouse the administration of sulphathazole holds the infection in check. Lately MacFarlane and Buchman have cultivated the organism of
developing chiefe embryo. In man infection in were may take place. The mother may be free from
toxoplasma infection, though giving immunity reactions to this organism.

It may be that the protozoan may produce an entirely different clinical picture. Pinkerton and
Henderson (1941) described two cases of acute exanthematic febrile disease similar to typhus, with atypical

bronchial involvement. In one of these fatal cases the bronchioles contained macroplages distended with these organisms. Organisms identical with toxoplasma have been found commonly in wild birds, in

mice, and in a monkey (M. mulatta) (Weiuman).
Frenkel recognizes four clinical types:—

(a) Congenital or neonatal meningo-encephalitis.

(b) Atypical encephalitis.(c) Post-encephalitic sequela.

(d) Pneumonitis associated with fever and a rash.

Under these headings acute, subacute and chronic stages are included. The acute infection is generalized, involving every organ and most bissues. The lesions are microscopic in size, "a explasma hodies are found to proliferate in macrophages, fibroblasts, reticular and sinusoidal cells. In the subscute the infection is represent a extraneural basies, but confinings active or progressive in CNS and eyes. The chronic form is found where there is clinical or laboratory evidence of toxoplasmosis.

In transplacental toxoplasmosis there is much direct and indirect evidence of antenatal toxoplasmosis

during pregnancy, and it is probably due to raptured pseudocytes infecting the totus via the placenta.

For diagnosis the skin-test of Frenkel is used; 0-1 ml. of 1: 500 dilution of supermatant fluid from centeilings frozen pertinened evaluate of Swiss mice, to which merthiolate to a luid dilution of 1: 10,000 has been added. Injected introdermally, the test is positive when after 24-18 hours an arcola persists which is bigger than 0.5 cm.

The slide neutralization test of Sabin and Feldmann consists of mixing equal parts of peritoneal exudate The since requestion less of short and redutant extracts of mixing quarters of personal extraction from infected inice and of subject's serum, incubating at 37° C. for one hour, examining under a high-power interescope a drop of the mixture to which one drop of saturated solution of methylene blue has been added. In the absence of antibody 90–100 per cent. of toxoplasma take the stain, whereas in its presence les; than 50 per cent. are stained.

A complement fixation is that of Warren and Sabin. The antigen consists of the clear supernatant fluid obtained by contribugation of pooled infected mouse peritoneal exudate, macerated by alternate freezing and thawing.

Summers has shown that sulphonamides and sulphones protect animals from infection. The protective action of aureomycin equals that of sulphathiazole.

On the other hand para-aminobenzoic acid antagonizes the protective action of sulphathiazole and 4: 4' damino diphenyl sulphone.

THE SPIROCHATES

These organisms, whose exact status in the scheme of nature is indeterminate. are included as a matter of convenience. They are now regarded as being nearer to plants than to animals, though formerly, on account of the method of transmission of blood-inhabiting species by lice and ticks, they were formerly classified as protozoa. Amongst spirochates which deserve consideration in this work are: Spirochata pallida (Fig. 234, 5) of syphilis; the corresponding closely-allied organisms of yaws, S. pertenuis, and of pinta, S. carateum. The organisms are

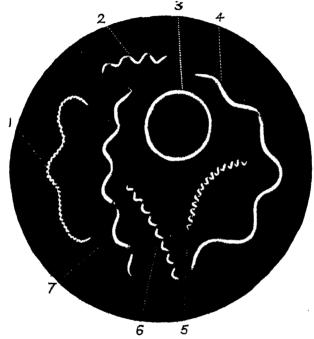


Fig. 234. Schema of different forms of spirochaetes. $\sim 3,500.$ (After Dobell; by courtesy of Wellcome Bur. Sci. Res.)

- Leptospira icterohemorrhague (Inada and Ido) Noruchi. Cause of spirochetal jaundice.
 Spirocheta carpygrata Werner. Commonly found in human faces, both in health and in disease (e.g. dysentery).
- 3. Human red blood-corpuscie on same scale.
- 4. Sprocheta recurrent's Leber (; Spirocheta obermeieri Cohn). Occurs in blood in relapsing fever, 5. Spirocheta pallida (Schandlan) Vuillemin (; Treponema pallidam Schandlan). Syphilis,
- 6. Spirocheta gracile Levadibi and Stanesco. Found on external genitalia, in health and in various diseased conditions.
- 7. Spirocheta refringens Schaudinn (emend.). Occurs in apphilitic lesions on external genitalia.

small, 5-14 μ in length, and are composed of numerous regularly disposed corkserew-like spirals of an amplitude of 1 \(\rho\). The extremities are pointed, the spirals wavy and regular. By aid of the electron microscope they are seen to possess flagella, and possibly an undulating membrane.

Somewhat similar non-pathogenic species are found in the mouth (S. dentium). throat (S. vincenti) and bronchi (S. bronchiulis). These organisms have been held responsible for "bronchial spirochatosis." Other somewhat similar species are found in the intestine (S. eugyrata) and were once thought to give rise to "spirochætal dysentery." Larger species with wider curves are recognized on ulcerating

surfaces—S. refringens, S. gracile on the external genitalia, and S. schaudinni in tropical ulcers.

The larger forms of *spirochæta* are more flexible and snake-like. They comprise the pathogenic blood spirochætes, the organisms of relapsing fever (S. recurrentis (Fig. 234, 4), S. duttoni, S. sogdianum, S. hispanica, and other allied forms). In birds (geese and fowls) similar parasites cause a fatal blood disease. The organisms are S. anserinum and S. gallinarum respectively.

The human blood spirochetes are transmitted by ticks (*Ornithodorus*) or by lice (*Pediculus*); those of birds also by ticks (*Argas*). All these spirochetes progress by corkscrew action resulting from revolution on the longitudinal axis.

Leptospira (Noguchi, 1917) includes the type Leptospira icterohæmorrhagiæ (Fig. 234, 7). These organisms measure 7-14 μ in length, with pointed ends and a spiral amptitude of 0.45 μ , and exhibit one or more gently indulating curves. There is no terminal axial filament or undulating membrane, but usually the end is bent inwards in the form of a crook. Two main pathogenic species (with variant forms) are recognized: L. icterohæmorrhagiæ of Weil's disease, and L. hebdomadis of seven-day fever. L. icterohæmorrhagiæ infests the urinary tract and liver of rats, and may possibly also occur as a free-living form in water (Zuelzer). It has also been found in the roof-slime of a mine in Scotland (Buchanan). It is highly pathogenic to guinea-pigs. L. canicola is found in dogs and is transmitted to man, especially in Holland. L. hebdomadis, on the other hand, occurs as a natural infection in the field-vole—Microtus montebelloi in Japan.

The spirochetes reproduce by simple transverse fission. No sexual phenomena have been observed in any spirochete and the life-histories of all are simple. Some observers have held that spirochetes have a granular phase during which they break up into minute granules which are capable of regenerating into spirochetes.

The organism of rat-bite fever—formerly Spirochæta morsus muris (p. 207)—is no longer classified as a spirochæte but as a spirillum. The correct terminology should be Spirillum minus (Carter, 1887). The synonyms therefore are: Spirochæta luverani and Spirochæta muris (Wenyon, 1906).

INTESTINAL AMŒBÆ

Entamaeba histolytica (Schaudinn, 1903). Synonym Endamæba dysenteriæ (Fig. 235)

Individuals of E. histolytica vary in size; usually the active forms are 20-30 μ in diameter; when active, they push out characteristic hyaline pseudopodia. The movements are in one direction, causing the protoplasmic mass to glide across the microscope stage like a "slug moving at express speed." (Fig. 69, p. 496.)

The cytoplasm is divisible into two zones: outer, with clear ectoplasm; inner, granular endonlasm.

The nucleus (4-7 μ in diameter) is usually invisible in the living state; when stained it shows a dot-like small central karyosome and peripheral chromatin in the form of fine granules; the nuclear membrane is a clear area marked by radial linin network.

Vacuoles are not present in active living individuals, but in degenerating trophozoites.

Large active entancebæ, vegetative or tissue-invading forms, are found in the intestinal wall, mainly in tissues at the bases of ulcers, where they multiply by binary fission, ingesting crythrocytes, leucocytes and tissue cells. These are the main distinguishing features between E. histolytica, E. coli and other non-pathogenic species. Further, in contrast to E. coli, E. histolytica rarely

ingests bacteria. Tissue-invading forms represent the most active phase of development. They are normally found in the walls of the intestinal ulcers, in dysenteric faces, and in metastatic lesions in lung, liver or other organs.

Amoebie dysentery can be transmitted to lattens, dogs, guinea pigs, monkeys and rats. Amoebic hepatitis has been produced in hamsters (Criectus auratus) by Reinertson and Thompson (1951). Jones (1946) and Goodwin (1947) have reproduced typical amoebic ulceration of the cacum of young white rats by intracacal injection of cultures of E. histolytica and also by injecting dysenteric



Fig. 235. -Entamoba histolytica, . 2,500. (After Dobell.)

Active anneboid form with invested red blood-corpuscien. 2, Uninnebate eyst. 3, Binucleate eyst.
 Quadrinucleate cyst. 5, Quadrinucleate eyst. small race, 6-6 μ in diameter. Note central distanct knryosome in the nucleu ;

stools of artificially infected kittens. Ulceration becomes evident in 24 hours. Carrera and Faust find guinea-pigs are easily infected by intrailed injection. Tobic has infected rabbits by intracesophageal inoculation. Though closely resembling E. muris, the common parasite of the rat, this animal has been found naturally infected with E. histolytica in U.S.A., Russia, and now in wild rats in London, in close association with human carriers of E. histolytica cysts (Neal). The importance of this subject has recently been re-emphasized by the same author (1951), who has addiced further evidence that the sewer-rat. R. norregicus, plays a prominent part in the dissemination of amorbic dysentery. From a study of the behaviour of E. histolytica in this rodent as well as in man. Hours now believes that E. histolytica can no longer be regarded as an obligatory tissueparasite; but that it also has a saprophytic coprozoic existence living as a commensal in the lumen of the gut, feeding on micro-organisms and other fiveal contents. As shown by Hoare a fair proportion of the entamedae contain foodvacuoles enclosing bacteria. This explanation tallies with clinical experience in symptomless cyst carriers whom it is easy to cure of this infection with drugs which exert no influence on the tissue-invading forms. There appears to be every gradation between these two stages in rats as well as, probably, in man.

Precystic forms.—Precystic forms develop from the larger entamæbæ by division, giving rise to small daughter-amæbæ. These are sluggish, with cytoplasm devoid of food vacuoles, and vary in size from 5 to $20~\mu$. The "minuta" form, $12-14~\mu$, is smaller than the tissue-invading form. They ingest bacteria and resemble a similar stage of E.~coli. The presence of food inclusions distinguish them from precystic amæbæ. "Minuta" forms hatch out normally from the large race of E.~histolytica living commensally in the fæces.

Cysts.—Cysts of E. histolytica in fresh material have a greenish refractile appearance. Sometimes on this account it is difficult to distinguish the nuclei, though chromatoid bodies may be clearly seen. It appears that there are two races: small, with mean diameter of cyst 7μ : large up to 11μ . The small has been considered non-pathogenic, whilst the large race is distinctly pathogenic, but this has not been absolutely proved. By some the small race is known as E. hartmanni from which small trophozoites hatch which may be mistaken for minuta forms. (Fig. 235, 2-5.) The mature cyst is quadrinucleate and commonly contains within its cytoplasm refractile chromatoid bodies. The cyst at first contains one, then two, and finally four nuclei, which retain the E. histolytica characteristics. A glycogen mass is also present, showing up brown with iodine, but both these features gradually disappear after the cysts have been voided in the faces.

Mature cysts do not undergo any further development in the intestine and, under normal conditions, do not hatch there, but acute infection of kittens can be readily produced by intra-rectal injection of material containing them. The process of conversion of the precystic form to the fully-mature cyst takes place in the lumen of the bowel and occupies a few hours. The quadrinucleate cysts can survive in the bowel for two days, but do not hatch until ingested by a new host. It has been suggested that some substance is present preventing further development. Fluid is apparently necessary for excystation; but from the quadrinucleate cyst a quadrinucleate ameba emerges, subsequently dividing by nuclear mitosis into eight unicleated individuals. This normally takes place when cysts are swallowed by a new host. The composition of the cyst wall renders it impervious to the action of the gastric juice, and excystation normally takes place in the alkaline contents of the small intestine. The generally accepted method of determining vitality of cysts is their capacity for taking up cosinstain. Dead cysts stain with weak cosin solutions, whilst living cysts do not.

Culture.—Cultivation of E. histolytica, in either active or cystic stage, on artificial media, can be effected on solidified egg slopes covered with horse serum and Ringer's solution. The addition of a small quantity of rice starch to each tube greatly aids the growth of amœbæ, which ingest the granules. The cultures are kept at 37° C. and should be re-inoculated every two to four days. Subcultures have been maintained for one hundred and fifty generations and are still capable of producing amœbic dysentery when injected into kittens. The student should bear in mind that the appearance of amœbæ in culture is somewhat altered by the starch granules they contain. Fuller and Faust demonstrated that dilution of aureomycin less than 1: 100,000 inhibits the growth of E. histolytica, and checks the growth of bacteria. It is concluded that this amœba grows in aureomycin as well as in penicillin or streptomycin cultures.

If starch is withheld from the cultures, if, in subsequent cultures, fresh blood is introduced, the amœbæ ingest red blood-corpuseles. Cysts in fæces stored

PLATE XXIII

INTESTINAL PROTOZOA (Unstained)

Row A. Entamæba histolytica.

- Active vegetative form with ingested red blood-corpuscles: granular endoplasm and clear cetoplasm.
- 2. Precystic form: note large nucleus with central karyosome.
- 3. Immature cyst with two nuclei and contained chromatoid rods.
- 4.- Mature cyst with four nuclei, vacuole and chromatoid rods.
- 5. Uninucleated eyst of the minuta form.

Row B. Entamarba coli.

- Active vegetative form with characteristic nucleus, blunt pseudopodium and protoplasmic vacuoles with food material.
- 2. Precystic form with characteristic nucleus,
- 3. Immature stage with two nuclei and vacuole.
- 4. Mature eyst with eight nuclei.

Row C. Endolimax nana.

- Active vegetative form with one nucleus and many small vacuoles.
- 2. Mature eyst with four nuclei.

Iodamæba bütschlii.

- 3.—Active vegetative form with one nucleus and vacuoles.
- 4. Mature eyst with one nucleus and large vacuole.

Row D. Giardia intestinalis.

- 1. -- Active form with sucking disc.
- 2. -- Active form (side view).
- 3. Cyst with four recently divided nuclei.
- 4. Four nucleated eyst (end-on view).

Row E. Trichomonas hominis.

1.—Active form with undulating membrane and supporting rod.

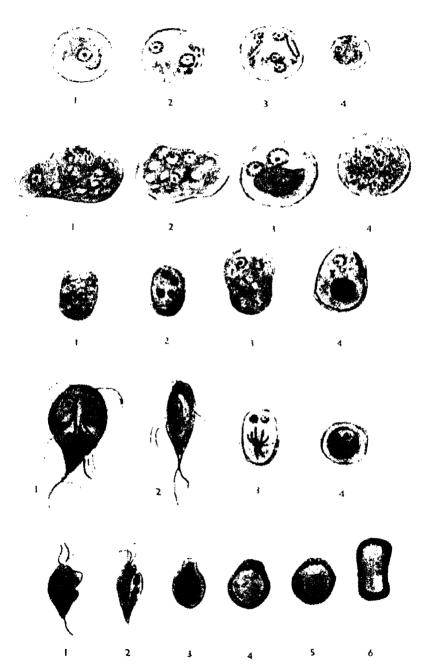
Chilomastix mesnili.

- 2.—Active form with peristome and contained flagellum.
- 3.—Pear-shaped eyst of above.
- 4, 5, 6. Various forms of Blastocystis hominis.



 $\begin{array}{ccc} \mathbf{HUMAN} & \mathbf{INTESTINAL} & \mathbf{PROTOZOA} & \mathbf{(unstained)} \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & \\ & & & \\$

PLATE XXIII



HUMAN INTESTINAL PROTOZOA (stained with Weigert's iodine)

(P. Manson Bahr)

PLATE XXIV

INTESTINAL PROTOZOA (Stained Weigert's Iodine)

Row A₁. Entamæba histolytica.

- 1.—Precystic form. Note diffuse iodine-staining substance.
- 2.—Immature cyst with two nuclei and chromidial rods.
- 3.—Mature cyst with four nuclei, iodine vacuoles and chromidial rods.
- 4.—Quadrinucleated cyst of the minuta form.

Row B₁. Entamæba coli.

- 1.—Active vegetative form with vacuoles and ingested food material.
- 2.—Precystic form.
- 3.—Immature cyst with two nuclei and vacuole.
- 4. Mature cyst with eight nuclei.

Row C₁. Endolimax nana.

- 1.- Active vegetative form with one nucleus and protoplasmic granules.
- 2.—Mature cyst with four characteristic nuclei and iodine-staining substance.

Iodamæba bütschlii.

- 3.—Active vegetative form with one nucleus and iodine-staining vacuoles.
- 4.--Mature cyst with one nucleus and iodinestaining vacuole.

Row D₁. Giardia intestinalis.

- 1 .- Active form with sucking disc.
- 2.—Active form (side view).
- 3.—Cyst with four recently divided nuclei.
- 4.—Four nucleated cyst (end-on view).

Row E. Trichomonas hominis.

1.—Active form with undulating membrane.

Chilomastix mesnili.

- 2.—Active form with peristome and contained flagellum.
- 3.—Pear-shaped cyst of above with nucleus and peristome.
 4, 5, 6.—Various forms of Blastocystis hominis.

at 4-6° C, remain viable and culturable as long as fifteen days. According to Dobell, symbosis exists between amoeba and a bacterium which is necessary for encystment (convivium). E, histolytica in culture is extremely sensitive to emetine, which destroys them within four days in the strength of one in five million. Americais may be reproduced in cats, dogs and rhesus monkeys (Macaca mulatla) and to a lesser extent in the guinea pig, rabbit and rat, by injection of cultures. An americai naturally found in anthropoid apes, macaques and other monkeys is probably identical with the human species. E. ranarum of the frog is morphologically identical. America dysentery in the kitten is severe. The mucosa of the whole of the large intestine is affected, and, in animals that survive, bacterial infection of the bloodstream, derived from the intestine, ensues. Metastatic amoebic abscesses of the liver are not infrequent in the cut, rarely in the dog.

Phillips (1950) has shown that cultivation of E. histolytica in the absence of bacteria fails, though "pure mixed" cultures with a single species of bacteria. can be obtained. An indirect approach to the solution of this problem has been attained by cultivating E. histolytica with living or killed Trypanosoma cruzi, These are grown in microtubes (4) 50 mm.) in a medium of thioglycollate proparation, horse serum and an overlay of N.I.H. medium containing a rich culture of trypanosomes. Culture of the amoeba, grown in thioglycollate-scrum medium in the presence of penicillin-inhibited streptobacilli are inoculated into test-tubes with the preceding medium containing T, cruzi. The amoshmtrypanosome cultures are maintained in 15 passages of subinoculation at intervals of 48 hours; penicillin being added to ensure elimination of the strepto-Microcultures of E. histolytica are started from single washed ameeba which are transferred by micro isolation to microtubes containing the above medium with trypanosomes, and in these cultures active annebæ can be seen for ten days. It has been proved that animals reared in sterile conditions cannot be infected with E. histolytica.

Rees, Reardon and Bartgis (1950) have shown that *E. histolytica* is capable of hatching from cysts in the absence of bacteria, when complex organic substances are added to the medium. Excystation proceeded very slowly in inorganic media without bicarbonates, was moderate in inorganic fluids with bicarbonates in glucose, but was best in media with bicarbonates and all organic compounds. The presence of amino-acids is essential.

Entamorba dispur is the name of a "physiological species," championed by Brumpt which is said to be non-publicgenic, albeit morphologically indistinguishable from P. histolyteat. This chaim is not admitted by most authorities.

ENTAMCEBA COLI (Grassi, 1879). (Fig. 236)

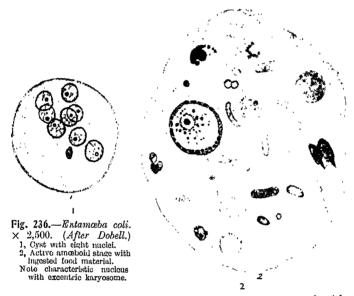
Unlike E. histolytica, this amoeba does not invade tissues; it is therefore a non-pathogenic species and a harmless commensal in the intestinal tract of man. A similar amoeba is found in monkeys and rats.

E. coli is a very common parasite in the tropics and, wherever sanitation is primitive, it is probable that no individual escapes infection. On the average, E. coli is larger than E. histolytica, but varies greatly. The active vegetative stage measures from 10 to 40 μ , but is usually 20–30 μ in diameter. It normally lives in the large intestine, does not invade tissues, but develops in intestinal contents, where it ingests bacteria, yeasts and other material.

Generally speaking, movements are much more sluggish than those of R. histolytica, and the individuals are less active. The organism does not move across the slide, but remains stationary. The ectoplasm is not clearly defined but is represented by a superficial clearer area merging into the endoplasm. This is extensively vacuolated, and food vacuoles contain bacteria, yeasts or

even cysts of other protozoa, such as *E. histolytica*, *Giardia* and *Isospora*. Red blood corpuscles or tissue elements are not ingested. In general, *E. coli* is faintly grey, contrasting with the greenish tint and higher refractive index of *E. histolytica*. Sometimes individuals show various fissures or rectangular vacuoles representing degenerative changes.

The nucleus, compared with that of *E. histolytica*, is larger, coarser and more easily visible in the living organism (Fig. 236, 2). The chromatin granules on the nuclear membrane are relatively coarse, and there are others on the linin network. The karyosome, larger than that of *E. histolytica*, is usually eccentric



in position, surrounded by a clear area intersected by linin network with chromatin granulcs. These nuclear characteristics are best seen in fresh specimens, but are obscured in degenerate individuals. *E. coli* reproduces by binary fission.

Precystic forms.—Before encystment the amœbæ undergo reduction in size, with the result that precystic forms are especially difficult to distinguish from those of *E. histolytica*, but are usually larger. Precystic forms are probably forme: by division of larger individuals.

Cysts (Fig. 236, 1).—The cyst wall is secreted round a spherical precystic amocha. Individual cysts vary greatly in size, from 10 to 30 μ . Like E. histolytica, E. coli is a composite species consisting of a number of races distinguished by the dimensions of the cysts.

The cyst is at first uninucleate, the nucleus having the same characteristics as that of the active form. It divides repeatedly by mitosis, the nuclei progressively diminishing in size as their number increases. The quadrinucleate stage is passed through very rapidly and is therefore rarely seen. The mature cyst is typically octonucleate. Immature binucleate and quadrinucleate cysts are occasionally seen, even supernucleate cysts with sixteen nuclei. The binucleate cyst frequently contains a large quantity of glycogen, which replaces almost the entire cytoplasm, but this usually disappears before the quadrinucleate stage is reached.

TABLE XI. DIFFERENTIAL CHARACTERS OF THE COMMONER INTESTINAL AMOEB E

Entama ba voli.	Entamwba histolytica.	Endolimax nana.
Size. 10–10 g. Morphology: No distinction between endo- and ecto-plasm.	20/30 μ. Granular endoplasm ; elear ectoplasm,	6–12 μ . Granular and rather vacuolated cytoplasm,
Ingests bacteria, other protozoa, etc.	Ingests red cells, tissue cells, etc.	Ingests bacteria and food granules.
fresh specimens. Coarse chromatin granules on		and massive, irregular karyosome.
with granular pseudo- podia. Multiplication: By binary fission in faces. Encystment and forma- tion of 1, 2, 4, and 8	Active movement with clear, blunt pseudopodia. By binary fission in intestinal wall. Encystment and formation of 1, 2, and 4 nucleated spherical cysts, 7–15 μ in diameter.	elear pseudopodia. By binary fission in facees, Encystment and formation of 1, 2, and 4 nucleated oval cysts
Chromatoid bodies typically not present in the mature cyst.	Chromatoid bodies especially present in the mature cyst.	Chromatoid bodies not present in the cyst.

Chromatoid bodies are usually not present, but, when they are, they appear as small granular, spicular or rod-like bodies, more especially in the binucleate stage. In the mature octonucleate form they may occasionally be seen as pointed threads or splinters, thus differing from the stouter bodies with blunted ends common in E. histolytica. When hatching, an octonucleate anneba escapes from the cyst and gives rise to eight uninucleate annebula.

The life history of *E. coli* resembles that of *E. histolytica*, except that the vegetative forms inhabit the faces, instead of the tissues of its host. This protozoau may be cultivated, but with difficulty, on the same media as are employed for *E. histolytica*. It is not affected by emetine.

Incidence.—E. coli is common in man in temperate zones as well as in the tropics, and found in about 15 per cent. of normal people.—It is most readily seen in dysenteric cases with diarrhea.—Some monkeys harbour a parasite closely resembling it.

Councilmania lafleuri is a name which Kofoid proposed for an amedia in human faces, thought to be distinct from E. coli, but actually representing an aberrant form of this species.

Entamæba gingivalis (Gros, 1849) (Fig. 237).

This amoba is of interest, not only for its occurrence in the mouth, but also because it was the first to be discovered in man. The claim that it might prove to be the cause of pyorrhœa alveolaris has been disproved. This species has been found in pulmonary suppuration by Sutliff and others (1951) by bronchoscopy. The importance of this lies in its differentiation from *E. histolytica*.



Fig. 237.—Entamarba gingivalis: active amedoid form with eccentric nucleus and ingested bodies. × 2,500. (After Dobell.)





Fig. 238.—Endolimax nana. × 2,500. (After Dobell.)

1, Active amæboid form. 2, Quadrinucleate mature cyst.

 $E.\ gingivalis$ is a small species with great variations in size, from 10 to 25 μ . As in $E.\ histolytica$, endoplasm and ectoplasm are sharply differentiated. The cytoplasm is occupied by food vacuoles, and peculiar inclusions of a greenish refractile appearance of undetermined nature, which may be the remains of salivary corpuscles or polymorphonuclear cells; there are also numbers of ingested bacteria.

The nucleus is similar to that of $E.\ coli$. It is $2\cdot 5-3\ \mu$, spherical and vesicular, but slightly smaller in proportion to the rest of the organism than in $E.\ histolytica$ or $E.\ coli$. The nuclear membrane is a definite structure, and is lined with peripheral chromatic granules.

E. gingiralis probably reproduces by binary fission, although all intermediary stages have not been studied and it is probable also that it does not form cysts.

Endolimax nana (Wenyon and O'Connor, 1917) (Fig. 238).

This is a non-pathogenic species commonly inhabiting the intestinal tract of man (mainly of the large and to a lesser extent of the small intestine), especially in the tropics, and it is of importance because the spherical quadrinucleate cysts resemble those of the small race of *E. histolytica*; moreover, it is found in 33 per cent. of dysenteric or diarrheic fæces, and is often very abundant indeed.

N. nana is a small species, 6-12 μ in diameter; it has a characteristic vesicular nucleus with a large irregularly-shaped karyosome. It ingests food granules and bacteria, but not red blood corpuscles or cells. Its movements are sluggish, but it may become quite active on a warm stage.

The cysts (Fig. 238, 2) are of approximately the same size and appearance as the active form. When fully mature they have characteristic nuclei and contain a few refractile granules, but are devoid of vacuoles or chromatoid bodies. Sometimes they contain glycogen, especially the binucleate forms. In shape they vary from that of a typical oval to a sphere. Small individuals measure 6 μ in diameter. Occasionally, they contain small filamentous rods or granules.

E. nana is certainly non-pathogenic and is not amenable to emetine. This species has been successfully cultured on serum and egg media.

Iodamaba butschlii (Prowazek, 1912) (Fig. 239).

Cysts of this species have long been known in man as "iodine," or "I. cysts," whilst similar organisms are found in the faces of monkeys and pigs.

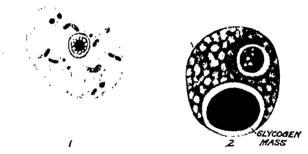


Fig. 239. Iodamæba bütschlii. < 2,500. (After Dobell.)

Active amæboid form with ingested micro occani ne. ?, Mature evel, "iodam eyek," contaming targe rodine staining glycogen ma...

I, bitschlii is small, intermediate in size between E, coli and E, nana, measuring from 9-20 μ in diameter, though smaller individuals, 5 μ in size, may occur. In form and habit it resembles small specimens of E, coli. The cytoplasm contains food vacuoles with bacteria and other food particles. There is no marked differentiation of ceto- and endoplasm. The movements are sluggish, like those of E, coli.

The nucleus, which is often indistinguishable in specimens containing many food granules, is large, being in diameter one fourth to one fifth of the whole organism. There is a large conspicuous karyosome which has a diameter of one third to one half of the nucleus.

The cysts are uninucleate, frequently irregular in outline, measuring 7–15 μ in diameter. There is a distinct cyst wall, and inside the cyst is a rounded refractile body with a number of small volutin granules. There is usually a large and dense glycogen mass which shows up clearly in iodine solution, and sometimes even two or three separated masses may be observed within the same cyst.

The cyst nucleus, eccentrically placed, is comparatively large, 2–3 μ in diameter, whilst the karyosome, which is centrally placed in the nuclei of the precystic stage, gradually passes, during encystment, to the periphery, showing up as a large compact mass in close contact with the nuclear membrane.

It is remarkable that very large numbers of cysts may be present in the faces without any evidence of free forms. The mature uninucleate cysts, save for the disappearance of the contained glycogen, do not undergo any further changes outside the human body.

It is estimated that *I. bütschlii* occurs in 5 per cent, of human faces, most commonly in the tropics, and is found, not infrequently, in association with *E. histolytica*. Both the active forms as well as the cysts are amenable to emetine and emetine bismuthous iodide. This amoba has been cultivated on egg medium and Locke's solution.

Pathogenicity.—A unique generalized ameriasis due to *Iodamarba bütsehlii* in a Japanese prisoner of war has been described by Derrick (1948). This

differed from any known infection of E. histolytica by the extent and bizarre nature of the lesions. These were—ulceration of the stomach, small intestine and colon. Metastatic foci were present in the brain, both lungs, gastric and mesenteric lymph glands, but not in the liver. In most of the lesions the amcebe occurred in enormous numbers. In all tissues they had the same morphology and varied from 3μ to 12 by 9μ , on an average of that of a leucocyte in sections. It is conceivable that a set of circumstances arose when the host's resistance was much reduced which caused the amcebe to invade the tissues—that there was a primary infection of the intestinal tract from which the amcebe spread to other organs. The invasion of vessels, arterioles, venules and lymphatics readily explains the widespread metastases. It is suggested that primarily there was a heavy infection of the fæces with I. bitschlii.

Dientamæba fragilis (Jepps and Dobell, 1918) (Fig. 240)

This is a small species which may measure $3.5-12 \mu$, but its usual size is $8-9 \mu$; it inhabits the large intestine of man and has also been found in monkeys (macaques in the Philippines).





Fig. 240.—Dientamæba frayilis, uninucleate and binucleate forms. × 2,500. (After Dobell.)

It is very actively motile, throwing out pseudopodia which are lobed and indented. Each anneba is typically binucleate. The spherical nucleus, measuring 0.8–2.3 μ , contains six chromatin granules. The two nuclei are connected by a thread (centrodesome). In fresh preparations the anneba rapidly degenerates and vacuoles form. It lives exclusively on bacteria and small micro-organisms, and is apparently amenable to emetine. No cystic stage is known.

Dobell has brought forward evidence that this amedia is closely related to the flagellate *Histomonas meleagridis* (the parasite of "blackhead of turkeys") which normally lives as a flagellate in the cacum, but can invade the liver, where it assumes the amedioid form.

Parasitism.—Most human amedoe are liable to be parasitized by a fungus—Spharita—consisting of a small spherical mass of coccus-like bodies, which are refractile and occur within vacuoles of the cytoplasm.

INTESTINAL FLAGELLATES

Enteromonas hominis (Fonseca, 1915) (Fig. 241, J-L)

Synonym.—Tricercomonas intestinalis (Wenyon and O'Connor, 1917).

This is a minute but very active pyriform flagellate, measuring 4–10 μ by 3–6 $\mu.$ The posterior end is attenuated to a fine point.

The nucleus is single and vesicular, and three flagella of equal length arise from a blepharoplast. A fourth flagellum runs down the margin of the body to the posterior extremity and ends in a terminal lash. The combined movements of all those produce a sort of "hovering effect" when in full action.

The cysts are small, oval, with a distinct cyst wall, resemble fungus spores, and contain iodophilic refractile bodies. This flagellate can be cultivated with comparative case on Locke egg-medium. There is no evidence of pathogenicity.

Embadomone's mestinalis (Wenyon and O'Connor, 1917) (Fig. 241, G-I).

A small but active flagellate, oval, $4.9~\mu$ by $3.4~\mu$, which inhabits the intestinal tract. There are two flagella: the anterior longer and thinner; the posterior projecting from a laterally-situated mouth (cytostome), at the anterior extremity, supported by a ridge. The flagella act independently and thereby impart a

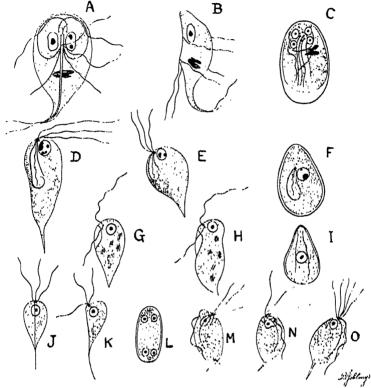


Fig. 241.- The flagellates of the human intestine. (× 2,000). (After Wenyon.)

A=C, diardia intestinalis, free and encysted forms; D ·F, Chilomastix mesmili, free and encysted forms; G-1, Embalomonas intestinalis, free and encysted forms; J · 1, Tricercomonas intestinalis, free and encysted forms; M-O, Trichomonas homanis, forms with three, four and five flagella.

peculiar jerky movement to the organism. The general shape is ovoid, with blunt anterior and pointed posterior extremities. The cytoplasm is vacuolated, containing ingested bacilli.

Cysts are pear-shaped, 4.5-6 μ in length, and appear structureless in the unstained state, but in iodine solution the nucleus can be discerned. This flagellate has been cultivated on egg medium. As in other members of this group, there is no evidence of pathogenicity.

Chilomastix mesnili (Wenyon, 1910)

Synonym.—Tetramitus mesnili (Fig. 241, D-F).

This flagellate resembles *Trichomonas hominis* in general shape and size and occurs in the large intestine. There are three long flagella, but no

undulating membrane or axostyle. There is a large mouth (cytostome), which occupies two-thirds of the body length, and contains a flagellum arising from a granule situated auteriorly to the spherical nucleus. The posterior extremity is attenuated. The cytoplasm contains numerous vacuoles and bacteria which form the main food supply. Division takes place by longitudinal fission. Individual organisms vary very much in length, but measure on an average 14 μ in length by 5-6 μ in breadth.

In freshly-passed frees, *Chilomastix* moves with active, jerky movements which distinguish it from the more deliberate rotatory action of *Trichomonas*.

Cysts.- "Lemon-shaped" cysts appear in formed stools and are 7 to 10 μ in length; they contain a single nucleus and vestiges of a cytostome. In fresh preparations they have to be differentiated from yeasts.

Infections with this parasite are very persistent, but there is no evidence of

pathogenicity.

C. mesnili has been cultured on artificial media.

Trichomonus hominis (Davaine, 1860). (Fig. 241, M-O)

This is the most common intestinal flagellate of man, inhabiting the execum

and large intestine, often in enormous numbers.

The body is pear-shaped, $10{\text -}15~\mu$ in length by $7{\text -}10~\mu$ in breadth. The spherical nucleus is at the anterior extremity and immediately in front of it are placed blepharoplasts from which three long flagella are directed forwards, whilst a fourth and stouter passes backwards to form the border of the undulating membrane, beyond which it is continued as a free flagellum. The cytostome is represented by a small aperture near the anterior end. A stiffening rod, arising from the blepharoplast, supports the undulating membrane. Running down the middle of the body is a second skeletal rod, or axostyle. The cytoplasm contains vacuoles with bacteria and food granules.

According to the number of flagella (3, 4, or 5), three varieties are recognized, although the triflagellate is the most common. Dobell thought that these varieties were merely strains of the same species. This flagellate progresses by lashing movements from the three anterior flagella, whilst the undulating membrane causes it to revolve on a longitudinal axis. The parasite is also capable of ameeboid movement, especially evident in degenerate individuals. Reproduction is by longitudinal fission, by duplication of the various parts. No cysts are known.

The abundance of T. hominis in diarrheic stools in the tropics has induced some observers to consider it pathogenic, and in one instance Wenyon found definite evidence of invasion of the intestinal nucesa by these organisms. Moreover, the closely allied T. cavice often causes ulceration of the large intestine in guinea-pigs.

On the whole, the pathogenicity of T. hominis in the intestinal tract of man is doubtful (see p. 540), and its presence in diarrhesic stools may be due to liquid

faces which constitute a congenial medium for this flagellate.

T. hominis can be artificially cultured on blood agar with Locke's fluid for many generations, but subinoculations are necessary every few days.

A somewhat similar species, T. clongata, is found in the mouth cavity, as well as on the tonsillar surface. A third form, T. vaginalis, is present in the vaginal

eavity of 10 per cent. of women.

Most gynecologists now regard T. vaginalis as a definite clinical pathogen, responsible for vaginitis, and the human analogue of T. fœtus, which causes inflammation of the genitalia of cattle. The two species are physiologically different. T. vaginalis is sometimes found in the male urethra (Liston, 1940) and can invade the epithelium and prostate. Feo (1946) has brought forward evidence that the male is the most important transmitter of this infection. It flourishes mainly during the reproductive period, but not, as a rule, in young

girls, or after the etimaeteric. It appears to multiply when the vaginal state is favourable, at $\rho\Pi$ 4, and a symbiotic association with a non-hamolytic streptococcus is suggested. The parasite disappears when the urine becomes alkaline. It is amenable to devegan, stovarsol and silver picrate (negatol). Stovarsol vaginal compound (8, V, C.- May and Baker) is much used: 2 tablets are inserted into the vagina for 12 days, after preliminary douching with normal saline.

Giardia intestinalis (Lambl, 1859)

Synonyms.—Giardia lamblia; Lamblia intestinalis (Fig. 241, A-C.)

This remarkable parasite lives in the upper part of the small intestine, particularly the duodenum. In shape it resembles a half-pear, split longitudinally. It measures 12-18 μ in length. The ventral surface is furnished with a concave sucking disc with a raised ridge at the anterior end, whilst the posterior extremity tapers into a fine tail and terminates in two flagella. There are altogether four pairs of flagella on the body, arising from as many blepharophasts; the posterior three arise from the margins of the axostyles. There are two of these stiff supporting structures which pass down the centre of the body. Two oval nuclei are situated within the sucking discs at the anterior end. The cytoplasm also contains a characteristically curved parabasal body in the lower half of the body. This flagellate swims rapidly, like a flat fish, swaying from side to side. Giardia reproduces itself by a complicated process of binary fission.

The cysts, which may occur in the faces in enormous numbers, are characteristic structures. They are oval, measuring about 14 μ . The body of the flagellate becomes rounded, while the various inner structures (flagella, axostyle, etc.) become detached and cannot always be identified, except for the crescentic parabasal. There are at first two nuclei, which divide, giving rise to four in the mature cyst. When examined in iodine solution, the cysts stain faint yellowish brown and the cytoplasmic contents shrink back from the thick wall.

Infections with giardia are very persistent, and it is found in the faces for many years. Under certain conditions it may possibly assume a pathogenic rôle, and this fact has been more generally recognized since it has been found susceptible to atchrin. It has been found in the gall-bladder at operation and quite commonly in duodenal contents obtained by intubation (see p. 540). This parasite has not been cultured. Similar species of giardia are found in rats, mice, dogs and other animals.

INTESTINAL COCCIDIA

Coccidia are intracellular protozoa with a life-eyele consisting of alternation of generations—an asexual cycle (schizogony), alternating with a sexual cycle (sporogony). A single zygote encysted as an oöcyst produces secondary cysts or sporocysts, which give rise to a number of sporozoites. The life history of a typical coccidium (Eimeria), which causes disease of the rabbit liver, closely resembles that of the malaria parasite. This fact led Pfeiffer in 1892 to predict, with some accuracy, the probable cycle within the mosquite. The sporozoites, liberated from the sporocyst, penetrate opithelial cells where they develop into schizonts, characterized by a vesicular nucleus and karyosome. The nucleus divides by repeated fission till a number of daughter-nuclei are produced and the schizont divides into as many merozoites. When the cell bursts, merozoites are set free and, entering other cells, develop either into schizonts or gametocytes, both male and female.

The male gametocyte develops by mitosis of the nucleus, forming microgametes, which are small, slender bodies. When the host cell bursts, these microgametes are liberated and enter the female cell (macrogamete). The fertilized cell (zygote) secretes a tough membrane and becomes an oöcyst.

The nucleus of the penetrating microgamete then fuses with the female nucleus (synkarion). The zygote breaks up into four sporoblasts, which, when enclosed by a tough envelope, are known as sporocysts, and within this the protoplasm divides into two sporozoites. In order to develop further, the occyst has to pass out in the faces and be swallowed by a new host, whereupon the tough membranes dissolve and sporozoites are liberated.

Eineria stiedw is a common parasite of the rabbit. A similar coccidium has been reported in the human liver, and named E. bugleri (Guiart, 1922). However, the authenticity of these findings is doubtful. Woodcock and Wenvon

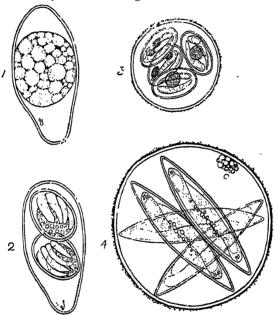


Fig. 242.— Occysts of coccidia found in human fæces. × 1,000. (After Dobell.)

1. Isospora hominis, undeveloped cyst. 2, Fully developed spores of same. 3, Eineria clupearum, fully developed occyst and spores.

4. Eineria sardiniæ, fully developed occyst and spores.

originally discovered coccidial cysts (*Isospora*) in human fæces in 1915. Dobell (1919) described cysts of the genus Eimeria as occasionally occurring in man.

Human Coccidiosis: Isospora hominis. (Railliet and Lucet, 1901.)
(Fig. 242, 1 & 2)

Synonym.—I. belli. (All authorities are not agreed that this synonym is correct. Hours considers that I. hominis and I. belli are distinct; the former probably a parasite of the dog, the latter of man).

Though undoubtedly a parasite of the epithelium of the small intestine, this coccidium is not seriously pathogenic, though it may be the cause of a debilitating diarrhora, in which the stools contain pus cells and Charcot-Leyden crystals. In addition there are cysts in the faces and associated cosinophilia, as in the cases described by Connal and the Editor. Nevertheless, the schizogonic cycle of development in the intestine is not yet known. The occysts are clongated, with tapering extremities; they vary in length from 18–33 μ and in breadth from

girls, or after the climacteric. It appears to multiply when the vaginal state is favourable, at pH 4, and a symbiotic association with a non-hæmolytic streptococcus is suggested. The parasite disappears when the urine becomes alkaline. It is amenable to devegan, stovarsol and silver picrate (negatol). Stovarsol vaginal compound (S. V. C.—May and Baker) is much used: 2 tablets are inserted into the vagina for 12 days, after preliminary douching with normal saline.

Giardia intestinalis (Lambl, 1859)

Synonyms.—Giardia lamblia; Lamblia intestinalis (Fig. 241, A-C.)

This remarkable parasite lives in the upper part of the small intestine, particularly the duodenum. In shape it resembles a half-pear, split longitudinally. It measures 12–18 μ in length. The ventral surface is furnished with a concave sucking disc with a raised ridge at the anterior end, whilst the posterior extremity tapers into a fine tail and terminates in two flagella. There are altogether four pairs of flagella on the body, arising from as many blepharoplasts; the posterior three arise from the margins of the axostyles. There are two of these stiff supporting structures which pass down the centre of the body. Two oval nuclei are situated within the sucking discs at the anterior end. The cytoplasm also contains a characteristically curved parabasal body in the lower half of the body. This flagellate swims rapidly, like a flat fish, swaying from side to side.

Giardia reproduces itself by a complicated process of binary fission.

The cysts, which may occur in the fæces in enormous numbers, are characteristic structures. They are oval, measuring about 14 μ . The body of the flagellate becomes rounded, while the various inner structures (flagella, axostyle, etc.) become detached and cannot always be identified, except for the crescentic parabasal. There are at first two nuclei, which divide, giving rise to four in the mature cyst. When examined in iodine solution, the cysts stain faint yellowish-brown and the cytoplasmic contents shrink back from the thick wall.

Infections with giardia are very persistent, and it is found in the fæces for many years. Under certain conditions it may possibly assume a pathogenic rôle, and this fact has been more generally recognized since it has been found susceptible to atebrin. It has been found in the gall-bladder at operation and quite commonly in duodenal contents obtained by intubation (see p. 540). This parasite has not been cultured. Similar species of giardia are found in rats, mice, dogs and other animals.

INTESTINAL COCCIDIA

Coccidia are intracellular protozoa with a life-cycle consisting of alternation of generations—an asexual cycle (schizogony), alternating with a sexual cycle (sporogony). A single zygote encysted as an oöcyst produces secondary cysts or sporocysts, which give rise to a number of sporozoites. The life history of a typical coccidium (Eimeria), which causes disease of the rabbit liver, closely resembles that of the malaria parasite. This fact led Pfeiffer in 1892 to predict, with some accuracy, the probable cycle within the mosquito. The sporozoites, liberated from the sporocyst, penetrate epithelial cells where they develop into schizonts, characterized by a vesicular nucleus and karyosome. The nucleus divides by repeated fission till a number of daughter-nuclei are produced and the schizont divides into as many merozoites. When the cell bursts, merozoites are set free and, entering other cells, develop either into schizonts or gametocytes, both male and female.

The male gametocyte develops by mitosis of the nucleus, forming *microgametes*, which are small, slender bodies. When the host cell bursts, these microgametes are liberated and enter the female cell (*macrogamete*). The fertilized cell (*zygote*) secretes a tough membrane and becomes an *oöcyst*.

The nucleus of the penetrating microgamete then fuses with the female nucleus (synkarion). The zygote breaks up into four sporoblasts, which, when enclosed by a tough envelope, are known as sporocysts, and within this the protoplasm divides into two sporozoites. In order to develop further, the occyst has to pass out in the fæces and be swallowed by a new host, whereupon the tough membranes dissolve and sporozoites are liberated.

Eimeria stiedæ is a common parasite of the rabbit. A similar coccidium has been reported in the human liver, and named E. bugleri (Guiart, 1922). However, the authenticity of these findings is doubtful. Woodcock and Wenyon

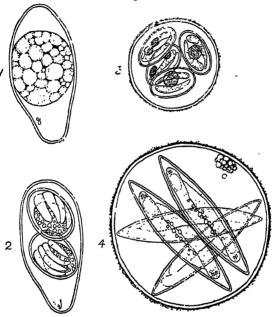


Fig. 242.—Oocysts of coccidia found in human fæces. × 1,000. (After Dobell.)

1, Isospora hominis, undeveloped cyst. 2, Fully developed spores of same. 3, Eimeria clupearum, fully developed oocyst and spores. 4, Eimeria sardinia, fully developed oocyst and spores.

originally discovered coccidial cysts (*Isospora*) in human fæces in 1915. Dobell (1919) described cysts of the genus Eimeria as occasionally occurring in man.

HUMAN COCCIDIOSIS: Isospora hominis. (Railliet and Lucet, 1901.) (Fig. 242, 1 & 2)

Synonym.—*I. belli*. (All authorities are not agreed that this synonym is correct. Hoare considers that *I. hominis* and *I. belli* are distinct; the former probably a parasite of the dog, the latter of man).

Though undoubtedly a parasite of the epithelium of the small intestine, this coccidium is not seriously pathogenic, though it may be the cause of a debilitating diarrhoea, in which the stools contain pus cells and Charcot-Leyden crystals. In addition there are cysts in the fæces and associated eosinophilia, as in the cases described by Connal and the Editor. Nevertheless, the schizogonic cycle of development in the intestine is not yet known. The oöcysts are elongated, with tapering extremities; they vary in length from 18–33 μ and in breadth from

 $12\cdot5-16~\mu.$ The cocyst wall is clear and colourless; the contained zygote is usually unsegmented, but occasionally segmentation into sporoblasts has been observed. Further development takes place in the faces; two ovoid sporoblasts become enclosed in sporocysts measuring 14 μ by 7–9 $\mu.$ In each eventually four sporozoites are produced.

Elsdon-Dew and Freedman (1953) recognize that there are at least two species infect man—one corresponding to *I. belli* (Wenyon) and the other to *I. hominis*

(Railliet and Lucet) as follows:-

I. belli may be passed at all stages of development, immature forms mature in up to 5 days. Occyst 30 $\mu \times$ 12 μ : sporocyst 11 $\mu \times$ 9 μ . Usually no occystic residual body; sporocystic residual body finely granular with limiting membrane, compact and centrally placed between four sporozoites.

I. hominis is usually passed fully developed. Occyst ball is usually absent. Sporocysts may be single or coupled in pairs, each being 15 $\mu \times$ 10 μ . Sporocystic residual body of coarse loosely aggregated granules appearing polar in position,

separate from the four sporozoites.

A single case of infection with *I. rivolta* (Grassi, 1879) has been reported and there is a possibility that *I. hominis* and *I. bigemina* (Stiles, 1891) are of the same species.

Cysts of the genus *Eimeria* have been seen in fæces, but they are not really parasitic in man, but are passed through the intestine after eating fish infected with *E. clupearum* or *E. sardinæ*. (Fig. 242.)

BALANTIDIUM

Balantidium coli (Malmsten, 1857), is a large protozoon belonging to the class ciliata. Oval in shape and of variable size, it is $30-200~\mu$ in length by $40-60~\mu$ in breadth. The average is 50-70 μ . Various races are recognized by the size. The body is clothed with a thick covering of cilia arranged in longitudinal rows. (Fig. 243.)

The nucleus is represented by a large kidney-shaped macronucleus with a small micronucleus closely approximated. The protoplasm contains two contractile and a number of food vacuoles. At the anterior end there is a peristome, leading into a mouth, or cytostome; posteriorly there is an anus, or cytopyge. Nutrition is effected by ingestion of solid particles, leucocytes and red blood corpuscles.

Bal. coli reproduces asexually by transverse fission. Conjugation takes place by exchange of certain nuclear elements and, when once this has been effected, the

conjugants once more separate.

The cysts (Fig. 243, 2) are ovoid, $50-60 \mu$ in diameter and are passed in the fæces. The enclosed balantidium loses its cilia, and sometimes two individuals are found in the same cyst. Transmission of infection takes place by means of cysts.

Bal. coli has been cultured in human serum diluted with saline. The presence of symbiotic bacteria is necessary, at 30–37° C, but frequent subinoculations have to be made.

Bal. coli not infrequently burrows into the intestinal mucosa and causes dysenteric symptoms—" balantidial dysentery," or "balantidiasis" (see p. 537). The balantidium is normally a parasite of the large intestine of the pig. Swine herds and pig-keepers are therefore particularly liable to infection. This parasite has been occasionally found in the mesenteric glands, as well as in the intestinal ulcers.

Bal. coli is a very active parasite and is frequently found in diarrheic as well as in bloody and mucous faces Balantidiasis in man has been recorded from

France, Germany, England, the Philippines and Rodriguez. It has also been found in chimpanzees, monkeys, ruminants, guinea-pigs, rats and other animals in captivity, often producing fatal results.

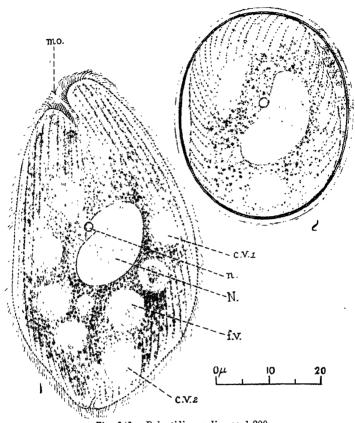


Fig. 243.—Balantidium coli. × 1,200. (After Dobell; by permission of Medical Research Council Report No. 51.)

Living individual; N., meganucleus; n, micronucleus; c.v.l, anterior contractile vacuole; c.v.2, posterior contractile vacuole; f.v., food vacuole; mo., mouth.
 Encysted form, showing nuclei, posterior contractile vacuole, and remains of cilia.

II. Medical Helminthology

TREMATODES OR FLUKES

FASCIOLA REPATICA (Linn., 1758).—Parasite of sheep, causing "liver rot.' Also found in "Jack" and "Cotton-tail" rabbits in U.S.A. and rats in Old World.

Distribution.-World-wide.

Characters.—Pale-grey with dark borders, it measures $2\cdot 3$ cm. by 8-13 mm.; large specimens in deer (7 5 cm.) are known as F. gigantica. The anterior extremity is narrow, containing the oral sucker; the ventral sucker is larger than the anterior and situated 3 mm. from the anterior extremity. Branched intestinal cæca with diverticula are present. The ovary is racemose, placed anterior to the testes in the posterior end of the body. The uterus is short and anterior to the ovary. An exsertile cirrus is present, and the genital pore is median.

The egg is operculated, 130–140 μ by 63–90 μ , ovoid, brown and bile-stained, and contains the ovum and yolk cells. A ciliated, eye-spotted miracidium develops in about three weeks, and enters freshwater snails: Limnaa truncatula (Europe), L. pervia (Japan), L. vicetrix (Cuba). Other snails are Succinea, Forsaria, Praticolella (a land-snail in Cuba) and Bulimus. In these it becomes a sporocyst, daughter sporocysts, rediæ (named after the Italian zoologist Redi) and cercariæ. Development takes two months. The cercaria is blunt-tailed and settles in grass or on bark, where it secretes mucus to form a cyst with two prominent suckers (metacercaria). Then it is eaten by the mammalian host. Metacercariæ excyst in the duodenum and migrate through the intestinal wall into the body cavity, then to the capsule of the liver to the biliary passages, where they grow to maturity. Man is usually infected by eating watercress.

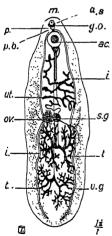


Fig. 244.1—Fasciolopsis buski. (After Odhner.)

Diagnosis.—This is effected by finding the characteristic eggs in the faces or in the duodenal juice. The blood shows cosinophilia and there is sometimes an afebrile colic.

Pathogenesis and treatment.—This fluke has been found as an erratic infection in 150 human cases: probably it is commoner than is supposed in Cuba, Venezuela. Argentine, Hungary, Switzerland, Germany, Greece, Tunisia, China and England. Flukes have been reported from the bile-duct by the Editor and by Walton, and they have been found in the portal vein and in subcutaneous abscesses.

Usually they cause little disturbance save diarrhœa, but they may produce cirrhosis of the liver. Epileptiform fits have been described in Lebanon, and also a buccopharyngeal infection known as "halzoun." In some instances there is cachexia and severe anæmia with cosinophilia. Emetine is said to be efficacious, 10–12 gr. being given in separate courses; so also are massive doses of magnesium sulphate with intravenous stibosan or glucantime. Mohr argues that the febrile

¹ The following is a key to the terminology of anatomy of trematodes, as illustrated in this and other figures: a.s., anterior sucker; m., mouth; p., pharynx; p.b., pharyngeal bulb; ac., acetabulum or ventral sucker: g.o., genital opening; ut., uterus; v.g., vitelline glands; ov., ovary: s.q., shell-gland; va., vagina; oo., ootype; ovd., oviduct; v.s., vesicula seminalis: r.s., receptaculum seminis; t., testis; v.d., vas deferens; cs., oesophagus; i., intestine; i.c., branch intestine; c.p., excretory pore; n.c., nerve cord: l.c., Laurer's canal.

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eosinophilic syndrome produced by the fluke is easily identified by irregular septic temperature, high eosinophilic leucocytosis, and enlargement of liver and spleen.

> FASCIOLOPSIS BUSKI (Lankester, 1857). (Fig. 244) A parasite of the pig which constitutes a reservoir for man

Distribution.—China, especially; India (Assam), Straits Settlements, Sumatra, Borneo and Siam. In China 5 per cent., and in Kamrup District. Assam, 50 per cent. of the population are infected.

Characters.—F. buski inhabits the small intestine, rarely the stomach; only a small number of those infected show symptoms. This is the largest human trematode, measuring 3 cm. by 12 mm., and 2 mm. thick. It is flesh-coloured, elongated and oval, with transverse rows of spines, especially numerous near the ventral sucker. The oral sucker is subterminal, but ventral in position. The ventral sucker, definitely larger, is placed close to the oral, and prolonged into the cavity dorsally and backwards, a feature peculiar to this species. (For details of the anatomy see Fig. 244.) The intestinal cæca are simple, with two characteristic curves towards the midline. The genital pore is median, placed anterior to the ventral sucker. Branched testes are found in the posterior half of the body; there is a branched ovary and a fine, tortuous, Laurer's canal.

Development in the freshwater snail resembles that of F. hepatica (Nagakawa, 1920).

The egg (Pl. XXVI, 1) is operculated, and yellow, measuring 120-130 μ by 77-80 μ . Eggs are found in large numbers in the fæces, the egg capacity of each fluke being about 25,000 per day. In water, after three to seven weeks, they hatch a ciliated miracidium which develops in freshwater snails—Planorbis cænosus, P. (Segmentina) schmackeri, P. (S.) hemisphærula (vel. largillierti), P. nitidella, Segmentina calathus, Hippeutes cantori, and Cyraulus saigonensis. A sporocyst is formed in three days, followed by the rediæ and daughter rediæ, which eventually produce cercariæ (the whole cycle takes two months).

The cercariæ, resembling those of F. hepatica, are oval, short-lived, lophocercous and measure 0.7 mm.; they have a well-developed digestive tract with a muscular bladder and collecting tubules. They encyst, as metacercariæ, on fresh-water plants, especially the outer cuticle of the water-caltrop (ling), Trapa (Salvinia) natans in China; T. bicornis in India; also Spirodela polyrhiza, to the leaves of which the cysts adhere. As many as twenty encysted metacercariæ may be found on a single leaf. In S. China the most important is the water-chestnut, Eliocharis tuberosa. The outer layers of the plants are torn off by the teeth. All the plants are grown in ponds in China, and fertilized by human fæces, thus affording an opportunity for infection; F. busk is therefore limited in distribution to that of these plants. The cysts, when taken into the mouth, pass through the stomach, excyst in the duodenum, and become attached to the intestinal wall.

Pathogenesis and treatment.—Often as many as 1,000–2,000 flukes are found in the small intestine, where they cause alternate diarrhox and constipation, with offensive pale-yellow faces and sometimes acute ileus. There is cedema of the face and also of the abdominal wall, genitalia and legs, and sometimes ascites. The pain may simulate duodenal ulcer. Death occasionally occurs from exhaustion.

Treatment.— β naphthol, ol. eucalypti, tetrachlorethylene and hexylresorcinol are all useful. For a child under seven 0.4 grm., and from 13 years upwards 1 grm. of the latter may be given.

CLONORCHIS SINENSIS (Cobbold, 1875). (Fig. 245)

Distribution.—Far East, especially China (Kwangtung Province in S. China, and Indo-China).

Characters.—This is a common parasite of man and also of the biliary passages of the dog, cat, pig, rat, mouse, camel and badger. It is found rarely in the gall-bladder of man, but often in the bile-ducts, pancreas, pancreatic ducts and duodenum. It is spatulate, tapering anteriorly, reddish, semi-transparent, and measures 10–25 mm. by 2–5 mm. The cuticle is smooth; the oral sucker is larger than the ventral; the intestinal caca are simple.

The genital pore is median and placed anterior to the ventral sucker. The

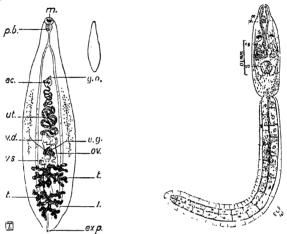


Fig. 245.—(1) Clonorchis sinensis, A, magnified; B, natural size. (Partly after Looss.) (For lotteding, see p. 936, footnote.)

(2) Cercaria of Clonorchis sincusis. (After Faust and Khaw. By permission of "The American Journal of Hygiene.")
OS=oral sucker. PH=pharynx. CG=cephalle secretory-gland. VS=ventral sucker.

testes are branched, and situated posteriorly one behind the other. The ovary is trilobate, with coils anterior to the genital glands. Vitelline glands are moderately developed in the mid-third of the body. Cross fertilization occurs; the spermatozoa develop before the ova; the sperms enter the female genital pore, pass into the immature uterus and thence to the spermatheca (Fig. 244, r.s.), where they are stored; the ova are fortilized in the spermatheca and then pass on.



Fig. 246.—Snail hosts of Clonorchis sinensis.

A, Bithynia striatula.

B, Bithynia longicornis (nat. size).

C, Bithynia fuchsiana.

The egg measures 20–30 μ by 15–17 μ (Plate XXVI, 5); it is operculated, yellow-brown, and one of smallest trematode eggs found in man, and is fully embryonated when discharged. It resembles an electric light bulb, with the knob at the bottom. It withstands desiccation but not decomposition. It can remain viable in water for five weeks, and is ingested by the snail before the

escape of the miracidium, which has a life-span of 20 minutes (Vogel). Development continues in Bithynia (Parafossarulus) striatula (Japan, Korea and Formosa), B. fusch siana, B. longicornis (China) (Fig. 246) and in Melania cancelluta. The miracidium pierces the cesophagus of the molluse, casts its cilia and soon becomes a sporocyst; later, the elongated rediæ grow within the sporocysts and burst into the peri-cesophageal sinus and move tailwards into the liver; the whole process taking three weeks.

The cercariæ (Fig. 245, 2) escape from the rediæ from the birthpore; they have two pigmented eyespots, a lophocercous blunt-ending tail, and burst through the space between the upper body surface and the shell, emerging into water. Within 24-48 hours they encyst, as metacercariæ, in the muscles and under-scales of fresh-water fish of genera Cyprinidæ and Anabantidæ (of which 34 species are susceptible). Cercarial glands excrete a histolytic substance which dissolves the skin of the fish, thus admitting percolating water. The metacercariæ secrete a viscous fluid which forms an inner true cyst, which in turn is encapsuled by a fibrous layer formed by the tissues of the fish. These are eaten half-raw, or pickled in soy sauce, by the Chinese. The adolescercaria, the fully-developed cyst, possesses a capsule protective against the gastric juice. In some species of fish—Carassius auratus and Eleotris swimhonis—the parasite is found under the scales; in others it is in the flesh, so that domestic animals which

eat the offal may become heavily infected while man escapes. The cysts withstand a temperature of 50-70° C. for 15 minutes. The cyst wall is digested by the succus entericus in the duodenum near the papilla of Vater, and the adolescercariæ escape and attach themselves to the mucosa. The young distomes at first have spines but these are soon lost. They attain maturity in 26 days. Attracted by positive chemotaxis, a small proportion of them reach the bile ducts, but 95 per cent. are digested and destroyed. The size of the resulting fluke is determined by the calibre of the bile-duct. Egg production is very large; in the cat 2,400 eggs are produced daily; but fewer in dogs. As many as 21,000 adults are found at autopsy (Sambuc and Beaujean). Life-span is 12 years. men are more infected than women.

The following is a complete list of the molluscs and fishes which may be intermediaries:—

MOLLUSCA

Fossarulus stachei, F. loczy, F. sinensis, Parafossarulus subangulatus, P. woodi, Pseudovivipara hypocrites, Hydrobiodes dautzenbergi, H. nassa, Bythinia striatula, B. longicornis, B. chaperi, B. moreletania. B. poeteli, B. misella, B. umbilicaris, B. morleti, B. goniomphalos, B. thatkeana, B. robusta, B. minor, B. truncata, B. dautzenbergiana, B. siamensis, B. funiculata, B. fuchsiana, B. delavayana, B. toucheana, B. lawis, Melania hainanensis, M. hongkongiensis, M. tuberculata, M. variabilis, Vivipara polyzonata, V. quadrata. (Walker, Miyanaga and Gaillard.)

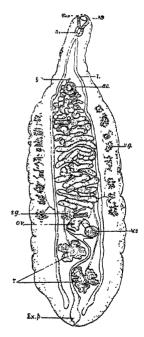


Fig. 247.—Opisthorchis felineus. × 9. (After Barker in "Arch. de Parasitologie.")

(For lettering see footnote on p. 936.)

PISCES

Hemiculter kneri, H. clupeoides, Acanthorhodeus atranalis, A. gracilis, Carassius auratus, Pseudogobio rivularis, P. sinensis, Pseudorasbora parva, P. fowleri, Eleotris swinhomis, E. potamophila, Paracheilognathus rhombea, Rhodeus sinesis, R. notatus, Culter brevicauda, Sacrocheilichthys nigripinnis, S. sinensis, S. morii, S. rariegutus, Macropodus opercularis, Biwia zezera, Xenocyprus davidi, Pseudiperilampus typus, Abbotina psegma, Leucogobio guentheri, L. striatus, L. coreanus, L. mayedæ, L. herzensteini, Ctenopharyngodon idellus, Acheilognathus lanceolata, A. limbata, A. cyanostigma, Labeo jordani, Hypothalmichthys nobilis.

For puthogenesis, see p. 795.

C. sinensis is often associated with carcinomatous changes in the liver and pancreas.

Opisthorohis felineus (Rivolta, 1884). (Fig. 247)

Distribution.—It is common in man in East Prussia (Kurisches Haff), Siberia, Annam and the Philippines; and in the dog, cat, glutton and pig.

Characters.—It inhabits the liver, panereas, bile duets and lungs (in Russia). It is lanceolate, and measures 8–11 mm. by 1–5–2 mm. The cutiele is smooth, the suckers equal in size and separated by 2 mm. (Fig. 247). The egg measures 30 μ by 12 μ (Pl. XXVI, 4) and is yellowish-brown with an operculum. At the posterior end there is a minute tubercular thickening.

Development (Vogel).—The snail is the intermediary host, usually *Bithynia* (*Bulimus*) tentaculata. The miracidium is fully formed in the egg and hatches in the snail, forming a sporocyst in the intestine measuring 1·2-1·85 mm. Rediæ are formed in one month, and then cereariæ which mature in two months.

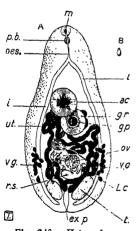


Fig. 248.—Heterophyes
heterophyes.
Greatly magnified: B. natural size

A, Greatly magnified; B, natural size. (For lettering, see p. 936, footnote.)

Cercariæ leave the snail by daylight. They are shaped like a tobacco-pipe, with tail membrane; they are phototactic, and stimulated by agitation. The secondary intermediary hosts are fish—the tench (Tinca tinca) and the chub (Idus melanotus). The cercariæ penetrate in 15 minutes, and grow to three or four times their original size, forming metacercarive. ingested by man, they pass through the stomach, are freed by the succus enterious, attracted by the bile and travel up the bile-duct in five hours. Infection is therefore contracted by eating raw fish. The entire life-cycle requires a minimum of four months. This fluke is not specially pathogenic, although 200 or more have been found in the body at autopsies.

Other species of little importance are O. noverca and O. viverrini (India and Siam), of which the normal hosts are the dog and civet cat respectively.

Heterophyes heterophyes (Siebold, 1852). (Fig. 248)

Distribution.—Egypt, China, Japan.

Characters.—It inhabits the small intestine of man in large numbers and also that of the fox, dog, wolf and cat, and imparts a coffee-grounds appearance to the intestinal wall. It is pyriform, grey and very small, measuring 1-1.7 mm. by 0.3-0.7 mm. The uterus forms a brown patch in the centre. The oral

sucker is subterminal and the ventral sucker is three times the size of the oral. The cuticle is thickly set with quadrate scales measuring $5\,\mu \times 4\,\mu$. There is a short prepharynx and long oesophagus. The intestinal cæca extend to the posterior extremity, converging close to the excretory vesicle. The vitelline glands are posterior, situated in two clumps; the genital pore is postero-lateral, in the vicinity of the ventral sucker, and consists of a muscular ring armed with 70 chitinous cuticular teeth. The testes are oval and posterior, the ovary globular and median. There is a receptaculum seminis as large as the ovary; uterine coils are not numerous. Seminal vesicle and Laurer's canal are present.

The egg measures 20–30 μ by 15–17 μ (Pl. XXVI, 3), being the same size as that of C. sinensis. Its greatest breadth is across the centre. There is no special ring to the operculum, which is light-brown and contains a ciliated miracidium when deposited. It hatches after ingestion by the appropriate snail.

Life-history.—H. heterophyes develops in brackish-water snails: Melania tuberculata, Cleopatra bulimoides; and in L. Manzala (Egypt), in a conical snail, Pironella conica (Khalil). The cercaria, resembling that of M. yokogawai, is oculate and lophocercous (membranous-tailed); it was formerly known as C. pleurolophocerca (Sonsino). The second intermediary is a fish—the mullet (Mugil cephalus) and minnow (Gambusia affinis); in Japan a species of Acanthogobius. There a brackish fresh-water snail (Tymphonotomus microptera) is the molluscan host.

Pathogenesis and treatment.—This fluke occurs in enormous numbers, attached to the mucosa of the small intestine; it may give rise to diarrhea. In Manila, heteropyes eggs are found in the walls of the intestines and in the myocardium and are said to produce symptoms resembling cardiac beriberi. Africa has recognized two other human species—H. brevicæa and H. taihokui. In Japan, in the vicinity of Kobe, H. katsuradai, a closely-related stouter species, is found. The flukes are readily removed by means of thymol and oleoresin of aspidium.

METAGONIMUS YOKOGAWAI (Katsurada, 1912). (Fig. 249)

Distribution.—Korea, Formosa, Japan and Balkan States, very common in Far East.

Characters.—This is found in the small intestine of man, higher up than H. heterophyes, and also in the cat, dog, pig and pelican. It is the smallest fluke parasitic in man, measuring 1.1 mm. by 0.42-0.7 mm. The cuticle is covered with small spines; the ventral sucker is deflected to the right with its long axis in the diagonal plane. There is a genital pore in front; the ovoid testes are posterior; the ovary and receptaculum seminis are situated medianly in front of the testes. The yolk glands are found in clumps in the posterior third. The uterus lies between the testes and the ventral sucker, and the seminal vesicle in front of the ovary.

Egg.—This measures 33 μ by 21 μ and resembles that of *C. sinensis*, but is more regularly ovoid (Pl. XXVI, 6).

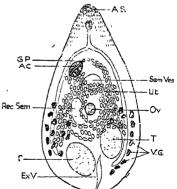


Fig. 249.—Metagonimus yokogawai. × 45. (Partly after Leiper.)

Sem. Ves., seminal vesicle; Rec. Sem., Receptaculum seminis; G.P., genital pore. (For other lettering, see p. 936, footnote.) The first intermediary is a molluse—Melania libertina and M. ebenina (50 per cent. of which are infected). Sporocysts, reduce and cercarize are formed; the last has an anterior end provided with armament. The tail is long and lophocercous, with lateral flutings, and is discarded on entering the fish—Plecoglossus altivelis. The metacercariae encyst under the scales; the infected fish is eaten raw by the Japanese.

Pathogenesis.—M. yokogawai causes a catarrhal condition of the intestinal tract and slight diarrhoa, but is easily removed by tetrachlorethylene.

Paragonimus ringeri (Cobbold, 1880)—"Lung fluke", and allied species: P. westermani and P. compactus. (Fig. 250)

Distribution.—Mostly Japan, Korea and the Philippines. It is found in man, dog, wolf, leopard and cat, especially in the lungs.

Characters.—P. ringeri measures 8-20 mm. × 5-9 mm. and is oval (almost round in section), reddish-brown and translucent. The anterior extremity is

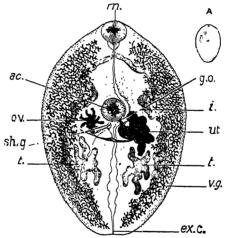


Fig. 250.—Paragonimus ringeri. (Partly after Looss.)

A, Nat. sive. (For lettering, see p. 936, footnote.)

rounded. The oral sucker is subterminal; the ventral sucker larger and placed anterior to the centre of the body. The pharynx and cesophagus are short, and the bifurcation of the intestine is anterior to the ventral sucker. The intestinal ceca run a zigzag course; the common genital pore lies close to the posterior margin of the ventral sucker. The body is bisected by a large excretory vesicle. The testes are tubular and racemose; the branched ovary may be either to the right or the left of the midline and posterior to the ventral sucker. The uterus is short, sac-like and lies opposite the ovary. The vitellaria are well developed, extending through the whole body. Laurer's canal and sholl-gland are present. The cuticle is studded with wedge-shaped spines and constitutes a reliable feature to differentiate closely-allied species. In P. westermani they are arranged singly, and in P. compactus they are in clumps, fewer and pointed.

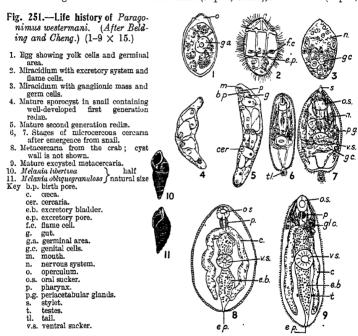
The egg is brown and operculated, measuring 90 μ by 55 μ . It shows a thickening at the pole opposite the operculum (Pl. XXVI, 2). That of P. westermani measures 85 μ by 55 μ and has the thickening at the posterior end, not so marked.

The egg of P. compactus is smaller, 75 μ by 48 μ .

FLUKES 943

Geographical distribution.—This differs with the species. P. ringeri is found in Japan, Korea, Indo-China, Siam and the Philippines; P. compactus and P. westermani in India and Malaya, North Africa, Southern Nigeria, British Cameroons and the Belgian Congo. A fourth species is P. kellicotti, from the pig, dog and cat in North and South America, and the tiger in Malaya; it has once been recorded in man.

Life-history.—This is complicated. (Fig. 251.) The eggs are first voided into cystic pockets in the lungs and then escape into water in the sputum and also in faces from swallowed sputum. A ciliated miracidium hatches in sixteen days to seven weeks and has distinctive characters. There is a ciliated covering in four rows at the anterior cone. The excretory pore forms a rosette. It enters snails of the genus Melania: M. tuberculata (Japan, China), M. libertina (Japan,



China), M. ebenina (Korea), M. obliquegranulosa (Formosa), and M. paucicincta, M. gottschei, M. extensa and M. nodiperda (Korea); in China, sometimes, Assiminea lutea; in Venezuela (P. kellicotti)—Ampullaria luteosoma. It develops in about 60 days into sporocyst and rediæ, each containing 20 cercariæ; the latter, ellipsoid and microcercous, have a short knob-like tail and measure 200 μ by 70-80 μ with an anterior stylet and body covered with spines. The cercariæ bore into fresh-water crabs and become metacercariæ in Potamon obtusipes, P. dehaani (Fig. 252), P. sinensis, Sesarma dehaani, Eriocheir japonicus (Fig. 253), Astacus japonicus; in Korea, Eriocheir sinensis and Cambaroides similis. In Venezuela the species is Pseudothelphusea iturbei; in the Philippines P. mistis. The cercariæ perish in 24 hours if they fail to penetrate the appropriate crustacean host.

The crab *E. sinensis* has been introduced into North German rivers in the bilge water of ships from China; it has multiplied enormously, but *Paragonimus* has not spread, because *Melania* is not present.

In the crustacean (the second intermediary) the metacercaria encyst in the liver, muscles and gills. In Japan, crabs are eaten raw, but in Korea and Formosa



Fig. 252.—Potumon dehaani. Half nat. size.

they are not eaten; the supposition is that the crustacean phase is not always a biological necessity. In Venezuela the appropriate snails and crustacea are present and 30 per cent. of dogs are infected, but man is not. When the meta-cercariæ enter the stomach of man, their cyst wall is digested and the adolescercariæ emerge, pass through the jejunum, traverse the abdominal cavity, penctrate the diaphragm, pleura and lungs, reach the bronchioles forming cystic cavities. (For Pathogenesis and Treatment, see p. 791.)

A trematode of less importance is *Echinostoma lindünsis*. Of this, a few cases from Celebes (Brug, Tesch, Bonne and Sandground, 1938-40) are reported, with flukes, sometimes in large numbers, in the jejunum. Reservoir host is the field rat. It causes diarrhea, abdominal pains and cosinophilia. *Development. First* intermediary: planorbid snails:—Anisus sarasinorum and A. convexiosculus.

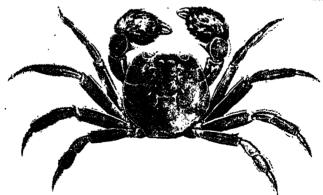


Fig. 253 .- Eriocheir japonicus, &. Quarter nat. size.

Second intermediary (metacercariæ), in snails:—Vivipara javanica rudipellis and two species of mussel:—Corbicula lindænsis and C. subplanata. All snails in Lake Lindoe, near heavily-infected village, were found to harbour large numbers of echinostome cercariæ, which have simple tails and a body resembling in miniature that of the adult worm. The eggs are straw-coloured, operculate and

measure 83–116 μ by 58–69 μ . Immature when passed in the fæces, they mature in 6–15 days. Filix mas and tetrachlorethylene treatments are specific. $E.\ ilocanum$ and the closely allied $E.\ malayanum$ (larger) are found in Singapore and Malaya. Natural host is the pig. The snail host is $Gyraulus\ prashadi$. Also $E.\ jassyens$ in Rumania, $E.\ recurvatum$ in Java and $E.\ sufrartyfex$ in Assam—all removed by filix mas. $Dicrocælium\ dendriticum\ syn.\ D.\ lanceatum$, of which the normal host is the sheep, is rarely found in man, in biliary tract in Germany, Czechoslovakia, Italy, France, Egypt. China. The eggs passed in fæces are fully embryonated, resist desiccation and do not hatch in water. They are ingested by land-snails— $Zebrina\ detrita$, $Hellicella\ candidula$, $H.\ itala$, $Torquilla\ frumentum$, $Cochlicella\ acita$ and others. $Plagiorchis\ javanensis$. Sandground (1940) found this species in small intestine of Javanese, together with $E.\ ilocanum$. It is a small trematode belonging to group normally infecting birds, fish, amphibia and bats. Development in snail— $Stagnicola\ emarginata\ angulata$. Another species is $P.\ philippinensis$, recovered at autopsy in Manila from the small intestine of a native who had eaten grubs of certain insects.

THE SCHISTOSOME GROUP

Distinctive characteristics.—These are unisexual (the sexes being separate) and inhabit the lumen of veins.

Schistosoma Hæmatobium (Meckel, 1856). (Figs. 254A and 254B)

Synonym.—Bilharzia hæmatobia (Weinland, 1858).

Distribution.—Africa, especially Cape Province; small foci in Portugal, Cyprus, Corsica, Palestine, Arabia, Madagascar, Réunion, Mauritius and Iraq. Also found for a short period in Perth, Western Australia, imported by returned soldiers from the South African War (1901).

Characters.—The male is 1.5 cm. by 1 mm., white and cylindroid, with oral, and more prominent, ventral suckers situated close together; the oral has a dorsal lip, longer than the ventral. Ventral infolding of the body forms gynæcophoric canal, which encloses the female. The outer surface, especially the dorsal, is beset with cuticular prominences (usually confined to the extremities of the worm), including delicate spines on suckers and larger tuberculations on the inner surface of the gynæcophoric canal. The ventral surface is beset with very fine spines. The male progresses along a vein carrying the female; the tuberculations aid progression against the blood-stream and along narrowing veins.

There are 4-5 testes which are round and placed posterior and dorsal to the ventral sucker (acetabulum). A similar number of vasa efferentia unite to form the vesicula seminalis at the genital pore which is placed median, posterior to the ventral sucker.

The female is darker, measuring 2 cm. by $0.25~\mathrm{mm}$; her filiform middle portion is infolded in the gynæcophoric canal, her anterior portion being free. The body is smooth with papillæ on the posterior end and on the suckers. An elongated oval ovary is found in the posterior half, anterior to the intestinal cæca. The oviduct arises from the posterior portion of the ovary, passes forward, and is joined by the vitelline duct. Vitellaria (yolk glands) are seen in the posterior part. The shell gland opens into the oviduct, which passes forward to a straight uterus. The genital pore is median, posterior to the ventral sucker; the anterior portion of the uterus contains several (20–30) terminal-spined eggs. The genital openings of both sexes face each other.

In both sexes the alimentary canal commences at the oral sucker, which is prehensile, and consists of an esophagus, with two dilatations which bifurcate, in front of the ventral sucker to form two intestinal cæca uniting into a median trunk in the centre of the body.

The excretory system consists of two longitudinal canals opening posteriorly, dorsal to the excretory porc.

The nervous system has an esophageal gauglion and commissure encircling the esophagus, and two longitudinal nerve cords running to the posterior end of the body intercommunicating by lateral branches.

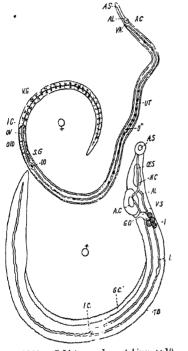






Fig. 254B.—Schistosoma hæmatobium. × 10. (After Looss.)

A.C., Ventral sucker; AL., bifurcation of alimentary canal; A.S., anterior sucker; G.G., gynecophoric canal; G.O., genital opening; L., indestine; I.G., union of intestinal cava; N.C., nerve cord; O'', terminal-spined ovum; GES., cosophagus; OO., cotype; OV., coray; OVD., oviduct; S.G., shell-gland; T., testes; T.B., tuberculations; UT., utrus; VA., vagina; V.G., vitelline glands; V.S., vesicula seminalis.

Habitat.—It lives in the venous system, the mesenteric, portal, vesico-prostatic, pelvic and uterine plexuses, the vesical veins, occasionally also in the vena cava and pulmonary veins. Sometimes 300 or more are present; they are more numerous still in experimentally-infected monkeys, being found specially in the submucosa of the bladder. They can be conveyed experimentally to rats, mice, guinea-pigs, monkeys, hedgehogs and armadillos (Pinto). S. hamatobium lives for 20-37 years and may produce carcinomatous changes in bladder. The sexes live apart while young, but, when mature, the female enters the gynæcophoric canal of the male. Bisexual and hermaphrodite males, as in S. spindale, are sometimes met.

Monkeys, mice, hedgehogs, and especially hamsters can be infected with this parasite in the laboratory, but experimental animals are much more difficult to infect with S. hæmatobium than with S. mansoni and the former takes longer to mature (80–100 days) than the latter (50 days) (Watson, 1948).

The egg is oval, measuring 150 μ by 60 μ , short, stout, and has a definite terminal spine (Pl. XXVI, 11). It contains the living, ciliated miracidium, the head of which lies towards the blunt end of the egg, but is active so that it can turn about.

When deposited in the tissues there is a thin and permeable clear space of dissolved cells in front of the egg, probably produced by a lytic substance secreted by the glands of the miracidium. The egg shell is permeable so that antimony can enter and kill the miracidium (Fig. 144, p. 713).

In freshly-passed urine the eggs appear brownish and contain active miracidia (Fig. 255) which develop early and are fully formed when they are deposited in the tissues. They escape by the transverse rupture of the shell, effected by osmosis in contact with water (dilution of urine with 10 parts of water), the shell being softened by a lytic ferment secreted by the miracidium. Temperature is important, as the eggs hatch more readily in warmth. The egg-shell enlarges before bursting. If the specific gravity of the urine is low, the eggs may hatch in urine within the bladder. The process is physical and will take place if the miracidium is previously killed by heat. The egg can remain alive in sterile urine, or moist fæces, for two or three weeks, but acid urine kills it. The miracidium is active and swims in water for 24 hours. It has an anterior papillary beak

but when swimming it changes shape and moves by means of cilia and muscular action. It has a primitive alimentary canal, two unicellular cephalic (salivary) glands, the ducts of which lead into the mouth, also germ cells, excretory tubules and four flame-cells. The nervous system is an oval, irregular mass, in the centre. The cuticle is composed of polygonal epithelial cells; the body has three zones, united by six or seven longitudinal strands.

After escape of eggs from the tissues the paired worms travel to the narrowest point; the female then leaves the male and penetrates into the smallest venules, where she deposits her eggs, which are then clamped in position by spasm of the veins. The female retracts after deposition of the egg, so that the spine is driven into the wall of the vein and the egg escapes into the tissues. (Fig. 260.) This is not generally accepted by all observers. According to Koppisch the eggs are engulfed by endothelial cells and this facilitates their passage through the vessel walls.



Fig. 255.—S. hæmatobium miracidium. (After Looss.)

The eggs of S. hæmatovium are often found in fæces (p. 709). Chesterman commonly found eggs in fæces (see S. intercalatum) in the Congo and Upper Egypt. Sometimes they are deposited in the lungs, brain and spinal cord.

Life-history.—Miracidia penetrate the air sac, tentacles and other portions of the snail, boring in by their papilla. If there are many, the snail dies. They are attracted by several species of Bulinus. The miracidium casts its cilia and travels via the lymph spaces to the liver or digestive gland. Infection of snails takes place in the warm season in Egypt, but not in the winter, and there is a seasonal variation in the number of snails. The two maximal periods in Egypt are May and December, with two marked reproductive periods—one in March and April—the other in October and November. During the Nile floods they die in large numbers, but reproductive activity stops temporarily during the winter closure of the Nile. On the return of the water into the canals the snails revive and commence laying eggs. The snail acquires immunity from slight infections. The liver of the snail is turgid, swollen, yellow or orange, and by

its appearance infected molluses may be recognized. The miracidium becomes an elongated, thin-walled sporocyst and subsequently daughter sporocysts permeate the gland. In about six weeks numerous bifid-tailed cercariæ appear within the sporocysts, and escape from it by a diurnal discharge from the pulmonary cavity of the snail, and are attracted by light. They cast off their tails on entering the skin of the host. Penetration is effected by the acid secretion of the glands, which cause a vesicular dermatitis. Most cercariæ die in transit, otherwise the infection would be colossal. For example, 30,000 may enter a mouse, but only 20 adults develop. The cercariæ adhere to the host by their ventral sucker and penetrate the mucous membrane of the mouth or esophagus. Thus people can be infected by drinking, e.g., women and children in Egypt. In bathing, movement of the water attracts the cercariæ to hold on to the skin.

(For anatomy of cercaria, see p. 955.)

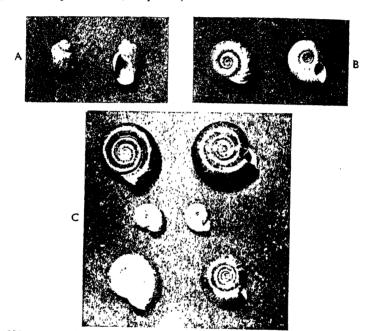


Fig. 256.— Intermediary hosts of Schistosoma hamatobium and of S. mansoni in Egypt, South America, and West Indies. (After Leiper.)

A, Bulinus contorius (nat. size). B. Bumphataria (Planorbis) bolssyr (nat. size). C. Australorbis olivaceus; B. bonssyi; A. glabratus (two-thirds nat. size).

On entering the body of man the larva are known as metacercariae, but within 24 hours they have entered the peripheral venules, through which they are transported to the right heart and to the pulmonary capillaries, squeezing through these to the pulmonary venules, they are carried passively through the mesenteric capillaries and enter the portal circulation. They are then known as Schistosomulæ. They mature in the liver in six weeks and produce terminal-spined eggs. Infection is easily effected in the laboratory by inserting the tail of a mouse in water containing cercariæ. In man and in animals, infection of the portal veins causes a deposition of hæmatin in the interstitial cells,

Intermediary molluscan hosts: Bulinus contortus, B. dybowskii (Egypt and North

Africa), B. innesi (Figs. 256 and 257) (Sudan), B. truncatus (Palestine), B. forskali (Mauritius and Kenya), B. globosus (Sierra Leone, Nyasaland), B. broichi (Tunis), B. (Physopsis) africanus (Natal), B. tropicus (S. Africa), Isodora oroidea (Zanzibar), Physopsis masuta (Kenya), Planorbis dufoucii (Portugal and Morecco), Melania nodicineta and M. tuberculata (Nyasaland). In the genus Bulinus the body of the snail contains red hæmoglobin. The shell is spiral, not operculated, and the opening sinistral (Fig. 257). In the focus in Bombay (see footnote, p. 702) the vector belongs to the genus Turbinicola (Ampullaridor).

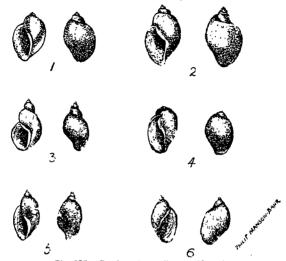


Fig. 257.—Fresh-water molluscs. Nat. size.

 Buliuns contortus;
 B. dyborsku;
 B. muesi;
 B. africanus—all intermediary hosts of S. hiematohiem;
 B. Physics who puen,
 a sinistral small apt to be mistaken for Buliuns;
 B. Limmed laurenti,
 a destruct

(Annandale and other conchologists consider that the three species B. contortus. dybowskii, innesi, are subvarieties of B. truncatus (Audouin, 1809) syn. B. contortus.)

Schistosoma intercalatum (Fisher, 1934).—Synonym Bilharzia intercalata. The eggs of this species were first found by Chesterman in 1923 when he drew attention to their importance. It was described as a new species by Fisher from the Upper Congo (Yakusu). Subsequently it was regarded as dubious, though reported from Gaboon by Zellweger, until the discovery was confirmed in every detail by Schwetz with cercariæ obtained from Stanleyville (1951). This species closely resembles S. hæmatobium, being half-way between it and S. bovis, differentiated mainly by the size and shape of the egg (Fig. 258). The eggs are found mainly in the fæces, very rarely in the urine; in this respect it resembles S. mansoni. The male has 4-6 testes. Schwetz succeeded in infecting mice with cercariæ from Physopsis africana sent from Stanleyville to Antwerp. From the fifty-first to fifty-eighth day he obtained adult schistosomes which resembled those described by Fisher. With miracidia hatched from eggs derived from mouse fæces and from their livers he succeeded in infecting P. africana in the laboratory. The snails began to shed cercariæ between the sixty-third and eightieth day. With these he confirmed the original discovery, produced further infections in mice and again recovered the adult forms. S. intercalatum then belongs to the same group as S. hamatobium. The eggs of both species have a

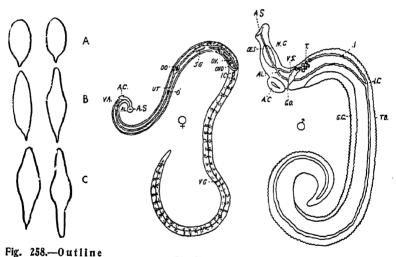
terminal spine, but those of S. hamatobium are round or eval, whilst those of S. intercalatum are elongated.

Schistosoma mansoni (Sambon, 1907)

Synonym.—Bilharzia mansoni (Fig. 259).

Distribution.—Africa generally—especially Egypt, Congo, West Africa, East Africa, Eritrea, Abyssinia, Zanzibar, Rhodesia, Tanganyika, Kenya, Uganda, Madagascar, Natal, Transvaal, South America (probably imported by African slaves), Brazil, Venezuela, Guianas, West Indies (Antilles, especially Antigua). In St. Kitts the green monkey (Cercopithecus sabreus), introduced from Africa, is naturally infected and constitutes a reservoir for man. Guineapigs, mice, hamsters, hedgehogs and the armadillo can also be infected in the laboratory. In Sierra Leone, infection is commoner in adult women than in children or in men.

Characters.—Male measures 1-1·2 cm. by 1 mm. and in its main structure is similar to S.hæmatobium, but with its ventral sucker and wart-like tuberculations larger and more pronounced (Fig.254, p.946). The intestinal canal bifurcates



drawings of eggs of
(A) S. hæmatobium;
(B) S. intercalatum:

(B) S. intercalatum; (C) S. bovis. (After A. C. Fisher.) Drawn to scale.

Fig. 259.—Schistosoma mansoni. × 10. (For lettering, see inscription to Fig. 254A; o', lateral-spined egg.)

at the level of the ventral sucker. The intestinal execa unite in the anterior half to form a long, single, intestinal tract. There are 8-9 small testes

with corresponding vasa efferentia opening into the vesicula seminalis. The size of the female is $1\cdot 2-1\cdot 6$ cm.; as in the male, the intestinal caca unite in the anterior half, where the ovary is also found, in front of the union of the intestinal caea. The uterus is short and contains a few (usually only one) lateral-spined eggs. The shape of the bulb of the shell gland determines the shape and position of the spine. The yolk glands occupy two-thirds of the body at the posterior end. The anatomy is otherwise as in S.hamatobium (q.v.). Hermaphrodite and bisexual males are found in hyperendemic infections and in unsuitable mammalian hosts.

Habitat.—It lives in the venous system, especially the inferior and superior mesenteric veins, the hæmorrhoidal plexus and the portal system. If at autopsy venous blood from the liver is squeezed out on the side of a glass vessel, the schistosomes adhere, and can be picked off. The eggs are deposited in the subterminal branches of the mesenteric veins where, aided by the lateral spine, the

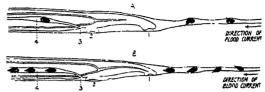


Fig. 260.—Diagram representing deposition of eggs by (1) S. mansoni and (B) S. hamatobium in blood-vessels, and their passage to exterior.

1. Anterior sucker; 2. posterior sucker, 3. vaginal orifice; 4. uterus with contained eggs

ovum escapes (see also p. 247). In the bowel some pass through the muscularis mucosæ via the capillaries; when present in large numbers, they produce acute dysenteric symptoms.

The egg measures 150 μ by 60 μ , the lateral spine 20 μ , but there is considerable variation. Immature specimens in intestinal lesions differ from eggs found in the fæces in being smaller. The miracidium is similar to that of S. hæmatobium, but may be larger. If the fæces are diarrhæic, the miracidium often escapes in the lumen of the bowel.

Life-history.—The sporocysts are convoluted thin-walled sacs within the head foot region of the snail and each contain 200–400 daughter sporocysts. Each miracidium carries 50–100 germinal cells which divide to produce anything up to 200–500 sporocysts.

The daughter sporocysts leave the mother sporocysts and migrate to the digestive gland. On reaching the location the daughter sporocysts enlarge and give rise to cercariæ. Most are derived from separate germinal cells carried by daughter sporocysts (a process known as polyembryony). The cercariæ were thought to differ in the two species, but this is probably not correct; but according to Faust, on the whole these cercariæ have somewhat smaller bodies and longer tails than those of S. hæmatobium. After penetration, they take six weeks to mature. The eggs are laid mostly in the portal system, eventually passing through the intestinal mucosa to escape in the fæces. Vogel has succeeded in infecting B. pfeifferi with a single miracidium. The proportion of the sexes eventually produced from cercariæ derived from a single miracidium is equal. Development takes place mostly in mollusc of the genus Planorbis, now known as Biomphalaria (Fig. 256 B.C.), viz., B. boissyi (Egypt), B. alexandrina and B. herbeni (Sudan), B. neosudanica (Nyasaland), B. pfeifferi (Sierra Leone, South Africa, Rhodesia), B. alexandrina tanganyicensis and B. choanomphala (Belgian Congo), B. philippici sub-angulata (Tunis), B. gibbonsi (Zanzibar), B. stanleyi (C. Kenya), B. adowensis (Abyssinia), B. rüppelli (Eritrea), B. cultrata (Venezuela), Australorbis glabratus, syn. P. guadeloupensis (Venezuela, Antigua), A. olivaceus (Brazil and Dutch Guiana), A. centimetralis (Brazil) and A. antiquensis (Antilles). It is probable that some of these species of Biomphalaria may prove to be geographical races. Cram and colleagues (1944) have demonstrated that Tropicorbis havanensis and Drepanotrema cultratus, widely distributed in Louisiana, Texas and Cuba, are good laboratory hosts of this parasite. Files and Cram suggest that there are physiological varieties of the same snail which affect their capacity to act as

intermediary hosts. Brazilian Australorbis glabratus differ from the same species from Venezuela and Porto Rico. The contrast between the susceptibility of Biomphalaria (P) pfeifferi from Liberia and B. boissyi from those in the W. Hemisphere supports the theory that this parasite was originally imported from W. Africa.

Papirmeister and Bang have demonstrated that when cerearize of *S. mansoni* newly emerged from *Australoibis glabratus* are exposed to diluted serum from monkeys or patients with schistosomiasis a precipitate forms around them.

Hyaluronidase is an enzyme which is elaborated by certain bacteria by means of which they are able to spread in the tissues. This ferment (Levine and others) can be detected in *S. mansoni* cercaria; but it is not claimed that it is the only enzyme concerned in cercarial penetration of the skin.

Schistosoma Japonicum (Katsurada, 1904)

Synonym.—Bilharzia japonica (Fig. 261).

Distribution.—Japan, China (Yangtse, North River, Yunnan), Upper Burma, South Philippine Islands (Samar and Leyte), Celebes: in restricted

Fig. 261. - Schistosoma japonicum, male and female. > 10.

A.S., Anterior suckers; G.C., gymaconboric canal; G.O., genikal opening; t., intestine; I.C., union of intestinal erea; G.S., Gesphagus; O.O., obtype; OY., Ovary; P.S., posterior sucker; S.G., shell-ghand; T., testos; VA., vagma; V.G., vitelline glands; V.S., vesicula scuinalis. endemic foci. This species occurs also as a natural infection in the cat, pig, dog, horse and cattle. It can be transmitted to monkeys, rabbits, hamsters, mice, rats and guinea-pigs.

Characters.—The male measures 9–12 mm, by 0-5 mm, and has 6–8 elliptical testes situated dorsally to the ventral sucker. The vasa efferentia join to form a common duet opening posterior to it. There is a large seminal vesicle. The posterior portion of the fluke widens out, and the sides overlap more extensively than in other species. There are no tuberculations.

The female measures 1-2 2-6 cm, by 0-3 mm, but shows variations in size. The ovary is centrally situated, and the intestinal excaunite immediately behind it. Well-developed yolk-glands extend to the posterior extremity. The uterus also is well developed and wider than in other species. It contains 50 or more eggs in two rows.

The general anatomy differs mainly from other species in the smaller size and absence of tuberculations. Suckers are placed close together at the anterior extremity, the ventral one (acctabulum) being pedunculated and funnel-shaped. Suckers and ventral surface are covered with small spines. Both

suckers are larger than those of *S. hamatobium*. The osophagus has *two* bulbs; the bifurcation of the intestinal canal takes place at the level of the ventral sucker, but the caea join more posteriorly, the united gut occupying usually nearly half the body length. The exerctory system consists of two longitudinal canals opening dorsally by an exerctory pore.

In utero the egg measures 60-80 μ by 40-60 μ , but when in fæces, 70-100 μ by 50-65 μ , is oval and practically spincless, but there is a rudimentary knob-like lateral spine in a small depression of the shell (Plate XXVI, 13). They are

extruded into the blood vessels, and are found chiefly in the intestinal walls liver, pancreas and mesenteric glands and brain. They may not be found in the fæces, but may be present in the duodenal contents. When they are passed into water with the fæces they hatch into ciliated miracidia. The cephalic glands of the miracidium are smaller than those of other species. According to Vogel, the maximum life-span of the egg is 21 days, of which development occupies 9-10 days. The mature miracidium inside the egg lives about 12 days.

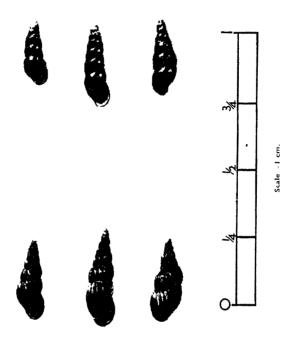


Fig. 262.—Molluscan hosts of Schistosoma japonicum.
Top row. Oncomelania nosophora. Bottom row: Oncomelania hapenyes.

Habitat.—Large numbers have been found in man at autopsy and 20,000 have been recorded in an experimentally infected horse. This schistosome inhabits the veins of the large intestine, the gastric, superior mesenteric, splenic and cardiac veins, occasionally also the pulmonary arteries, but rarely any others. It commonly inhabits the veins of the small intestine and in this respect differs from the other two human species.

Life-history.—This is similar to that of the preceding species. Losing its cilia, the miracidium becomes a sporocyst in the liver and hermaphrodite gland of a snail, Oncomelania (several species, Figs. 262, 263). The delicate, elongated, finger-like sporocysts each produce 50 or more daughter-sporocysts. Cercariæ are similar to those of other species, but are said to be smaller (0.48 mm. by 0.05 mm.) (Fig. 265). They are produced sixty days after infection, are

phototactic and unable to survive a temperature above 50° C. or below 2° C. Discharge of cercariæ from *Oncomelania quadrasi* takes place largely at night and continues for 2–3 consecutive nights (Ingalls). The critical factor appears to be the



Fig. 263.—Oncomelania hupensis with operculum.

alkalinity of the water— $pH\ 7\cdot 0$. The oral sucker is greatly developed. The cerearize escape into water, and penetrate the skin; subsequently minute flukes (schistosomula), measuring $150\ \mu$, can be found in the liver. They attain maturity in 30 days, and in 35 days eggs appear in the fæces. These reach the lungs through the pulmonary arteries, and travel via the mesenteric arteries and veins and portal veintto the liver. The molluscan host belongs to the genus Oncomelania (Gredler, 1881), sometimes also known as Katayama, Hypsobia, Blanfordia and Hemibia. O. nosophora (Japan and chiefly China); O. formosana, which has a

relatively shorter and broader shell (South Formosa); O. hupensis (Fig. 263) (Yangtse Basin, China); O. (Katayama) tangi (Fukien, China); O. (Blanfordia) japonica (Japan, Sadi); and O. (Hydrobiopsis) quadrasi (Philippines).







Fig. 264.—Operculum and shell of Oncometania nosophora. (After Robson.)

A, Operculum, × 12, diagrammatic to show scheme of coiling. B, Oral aspect of shell, × 4. c,

Lateral aspect of shell, showing labial swedling, × 1.

Oncomelania has a long narrow shell with multiple whorls, the breadth increasing from the apex downwards. It is 5-12 mm. in length. The basal whorl is never broader than the one above it. Its apex, though frequently worn, is sharp, and the mouth of the shell ovate. The outer lip is sharp and the external surface coarsely ridged. The operculum is thin, transparent and ovate. There is a spiral figure on the inside (Fig. 263). All these snails live in damp places, not in water, burying themselves in the earth. They favour slow-moving water-courses rich in vegetation. At the northern limits of their range they hibernate When climatic conditions are unfavourable they continue to harbour cercariæ but do not void them. In Japan and the Philippines Oncomelania is closely simulated by Blanfordia, but the number of whorls is smaller and the contained molluse has a proboscis-like snout.

An important factor in the life history of O. hupensis is that the eggs are covered with a mineral slime which is derived from a clay in its normal habitat and without which it cannot multiply.

By supplying this clay the snail is easily maintained in the laboratory and can be infected with S. japonicum. In America it has been found by Berry and Rice that a common water snail—Pomatiopsis lapidaria—can transmit this parasite.

Vogel (1941) succeeded in producing hybrids between S. japonicum and S. mansoni. The eggs were not deformed, but retained the shape of those normally passed by the mother fluke.

OTHER SCHISTOSOMIDÆ

S. bovis (Sonsino, 1876) is found in sheep and cattle in South Africa, South

Europe and Malaya, and occasionally accidentally in man on the shores of L. Victoria, Uganda.

The egg differs from that of S. hæmatobium in being longer and narrower, with a terminal spine; it occurs in fæces and urine. molluscan host is Physopsis nasuta (Kenya).

S. mattheei (Veglia and Le Roux, 1929), but probably synonymous with S. boris, is found in association with S. hæmatobium in the vesical veins of man (Southern Rhodesia, Blackie and Alves). The egg measures 240 μ by 70 μ and is seen in urine and fæces. The male measures 1.8 cm. by 1 mm.: the female 1.7 cm.-2.5 cm. A baboon is the reservoir host.

The eggs of S. incognitum (Chandler, 1926) have been seen in the fæces of man in Krishnagar (Bengal); they resemble those of S. indicum (of cattle), but are smaller and less regular, resembling those of S. suis.

Schistosome cercaria. 1—These consist of a body and elongated forked tail (Fig. 265), measuring 0.48 mm. in total length. The head and tail are approximately of equal length. The cuticle is beset with microscopic spines. They have an anterior urn-shaped oral, and median muscular, ventral sucker; the former is larger. The central part of the body is occupied by the oral glands and a mid-line esophagus, on either side of which are the ducts of conspicuous peri-acetabular glands, opening by small retractile papillæ surrounding the mouth. It has been shown that the peri-acetabular glands are connected with the penetration of the skin. Contraction of the circular muscles compresses the ducts and expresses the secretion, enabling the cercaria to burrow into the tissues. The mouth opening is small, oval and placed on the anterior surface. The œsophagus is situated at the lower pole. The ventral sucker is covered with small spines pointing to the There are five periacetabular periphery. glands, having large clear cells, with conspicuous nuclei and acidophil protoplasm. There is a primitive nerve ganglion anterior to the central sucker. The posterior genital centre consists of a mulberry mass of cells.

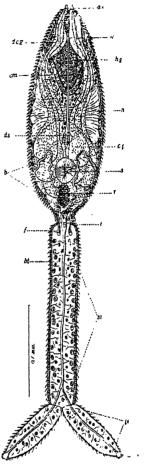


Fig. 265.—Cercaria of Schistosoma japonicum, ventral view. \times 240. (After Cort, "Univ. of California Publications in Zoology.")

as, Anterior spines; b, excretory bladder; cg, cephalic glands; cm, circular muscles; dcg, ducts of cephalic glands; ds, digestive system; exp, excretory pore; f, flame-cell; hg, head-gland; i, island in excre-tory bladder; lt, lobe of tail; m, mouth; n, nervous system; st, stem of tail; r, rudimentary genital cells; s, ventral sucker.

¹ As many as 300,000 may be discharged, and the cercarise are all of one sex. The metacercarise (or schistosomulae) are carried to the lungs and remain there long enough to squeeze through the capillaries in order to reach the pulmonary veins. Only those which leave the aorta by the coeliac axis or mesenteric arteries and reach the liver via the portal vein survive.

The exerctory system consists of four pairs of flame-cells on the margins of the body; the canals form collecting tubules of greater calibre running forwards and backwards, to meet at the posterior end of the body. The duct is continued through the tail where there is one pair of flame cells.

All cercariæ are "phototactic," emerging from the snail in sunlight between 9 a.m. and 2 p.m., and do not emerge on dark days; some 50 to 1,000 may be discharged daily. The optimum temperature for most species is 32-33° C., but for S. mansoni, 15-35° C. An abundant supply of oxygen is necessary for their survival. The lips of the oral sucker are extended or retracted to assist in entering skin. Cercariæ cannot feed. In water they swim with ease, moving by the tail and body, in a circular movement propelling towards the tail. They rest with the prongs of the tail on the surface, and then slowly sink; they then absorb oxygen through the tail, then rise again. The total life-span is 5 days: they are infective for 3, becoming motile when the water is disturbed. They adhere to the side of the vessel by the ventral sucker and, when they fix on to an object, they clongate. Movement on a fixed surface is effected by releasing the ventral sucker, contracting the body, and then affixing themselves by the oral Warmth appears to be the chief factor in attraction to a host. When they contact it, they cast off their tails, pierce the epithelium, lose the cephalic glands, and become a schistosomulum. The cercaria come into contact with the skin at the surface film and, as the water evaporates, they enter the skin. Adult schistosomes are found in the portal vein within six weeks.

There is no general agreement on the different minor details in the structure of the three human species; probably there are individual differences in various batches. The average size is 0·4·0·5 mm, in total length; on the whole, cercariæ of S. japonicum are smaller than others, with measurements as follows: Body, 100–160 μ in length by 40–66 μ in transverse diameter; tail trunk, 140–160 μ in length by 40–66 μ in diameter; furei, 56–75 μ long. All kinds have 5 or 6 pairs of salivary-mucin peri-acetabular penetration glands. Innumerable trematode cercariæ are found in freshwater smalls in tropical countries. The life-history of many is unknown. All schistosome cercariæ of man, mammals and birds have forked tails.

C. elvæ is found in Lake Michigan and in several Minnesota lakes and is a schistosome cercaria (non-mammalian) emerging from Limnaa stagnatilis var. appressa (see p. 670). It produces a papular cruption in bathers. C. ocellata (Taylor and Baylis) produces "swimmers" itch" in Lake Routh, near Cardiff, emerging from L. stagnatilis at certain times of the year. It is probably a schistosome parasite of a water fowl. Other species are C. douthitti, C. physellæ and C. stagnicolæ. The rash consists of blotchy papules with a central puncture (p. 670). In Malaya and India a similar rash is produced sometimes by cercaria of Schistosoma spindale of the Indian water buffalo.

AMPHISTOME TREMATODES Gastrodiscoides hominis (Lewis and MacConnell, 1876)

Distribution.—Malaya, Assam, India, Burma, Cochin China, British Guiana. In Kamrup District, Assam, 41 per cent. of the population are infected; in Burma 5 per cent. The normal host is the pig or the mouse-deer.

Characters.—The fluke is reddish from hamoglobin pigment. When alive, it is very expansile and can elongate to 1 cm. Preserved specimens measure 5-7 mm. by 3-4 mm. at the widest point. The anterior end is conical, the posterior discoidal flattened ventrally to form a concave disc. Prominent genital papillæ are seen, and the common genital pore is 2.5 mm. from the oral

¹ Faust stated that the cercaria of 8. hemutobium has 2 anterior pairs with oxyphilic and 3 posterior pairs with basphilic granules; those of 8. mansoni 2 anterior oxyphilic and 4 posterior basephilic; and those of 8. japonicum 5 pairs with line oxyphilic granules.

sucker. The ventral sucker (acetabulum) is ventrally situated in the caudal portion and measures 2 mm. in diameter. The cuticle is smooth. The alimentary canal consists of a pharynx with two pear-shaped pharyngeal pouches. The cesophagus is 1 mm. in length, and ends in a muscular bulb where the bifurcation of the intestine takes place and cæca run back to the edge of the acetabulum. There are two lobulated testes placed diagonally between the intestinal cæca. A seminal vesicle is present, but no cirrus. The ovary lies in the midline, posterior to the testes. An ovoid shell gland is placed near the ovary with a receptaculum seminis anterior to it. The uterus is short. Laurer's canal is present. The vitellaria lie in the mid-third. The egg measures 152 μ by 60 μ and has an operculum. Development outside the body takes place in a snail, probably Cleopatra bulimoides.

This fluke lives in the execum in large numbers and usually produces no symptoms. Thymol, carbon tetrachloride and tetrachlorethylene are effective in treatment.

Pseudodiscus (Watsonius) wutsoni has been found in large numbers in a negro in South West Africa (1904). Its normal hosts are monkeys of the genera Cercopithecus and Papio.

CESTODES (kestos = a girdle) or TAPEWORMS

The head of these worms develops from the end of the embryo opposite to the head, and shows independent co-ordinated movement. The strobila, or segments, have their own musculature, which relieves the strain on the head. The worms can live for several years. They absorb nutriment through the cuticle. They are hermaphroditic, the male segments fertilizing the adjacent female. Male organs develop before the female.

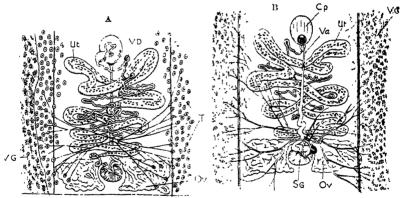


Fig. 266.—Mature segment of Diphyllobothrium latum. (After Sommer and Landois, in Brumpt's "Précis de Parasitologie.")

A, Dorsal, or male aspect. T, testes; V.D., vas deferens; V.G., vitelline glands. B, Ventral, or female aspect. C.D., cirrus pouch; Ov., ovary; S.G., shell-gland; U.T., uterus; Va., vagina; V.G., vitelline glands.

Human cestodes are divided into two orders:

- 1. Pseudophyllidea, with slit-like suckers, oval head, two long grooves with muscular walls, no hooks, and the genital orifice on the flat surface.
 - 2. Cyclophyllidea, cup-like, or round suckers; genital orifice marginal.

PSEUDOPHYLLIDEA DIPHYLLOBOTHRIUM LATUM (Linn. 1758)

Synonym.—Dibothriocephalus latus (Fig. 266). "Broad Tape Worm."

Distribution.—It lives in the small intestine of man, the dog, cat, bear. walrus, sea-lion, fox, mongoose, mink, and pig, and is found in Sweden, Russia. Switzerland, Rumania, Turkmenistan, Japan, Madagascar, the Central African lakes, and in the rivers Erne and Shannon in Eire (Ireland). In recent years it has been introduced into several big North American lakes, especially Lake

Michigan, where it is known as the

"Broad fish tapeworm."

Characters.-It is greyish and more translucent and less fleshy than Tænia and may attain a length of 10 metres, lying coiled up in the small intestine. Multiple infections are common. The scolex (3 mm.) has no rostellum or hooklets, but two slit-like suckers with longi-The neck is tudinal grooves (bothria). thin; the proglottides number 3,000-4,000. It lives 5-13 years and the number of worms corresponds to the plerocercoids individual swallowed (Leiper). Mature segments are broader than they are long. (For details of anatomy of male and female elements, sce Fig. 266.)

The egg is operculated, with a brown shell, measuring 70 μ by 45 μ (Pl. XXVI, 21). No segments are passed in faces (unlike Tania). The eggs are found in vast numbers in the fæces, occupying one third of their bulk. The yolk-cells are tightly packed, crowded with steelgrey granules (thus differing from trematode eggs).

Life-history (Fig. 267), Rosen and Janicki, 1918.-The egg is passed in water; when the operculum is lifted, coracidium ciliated six-hooked emerges; resembling a ball (22-30 μ), it swims by means of its cilia, but dies in 24 hours. Normally it is swallowed by freshwater crustacea, the first intermediary—Cyclops strenuus, Diaptomus gracilis: D. graciloides or D. oregonensis, D. silicis and D. silicoides in U.S.A. The outer layer is then digested. The hooks tear a hole in the gut wall; it passes into the body cavity and may kill the cyclops. Lying outside the gut wall, it becomes the procercoid larva (Fig. 267, D, E, F) which is ovoid, 50-60 μ long, with a terminal spherical appendix and six hooklets in the terminal appendage or cercomer. At most two of these are found

in one cyclops, which is then swallowed by fresh-water fishes of many species, the second intermediaries—pike, perch, salmon, trout, grayling; in Africa the

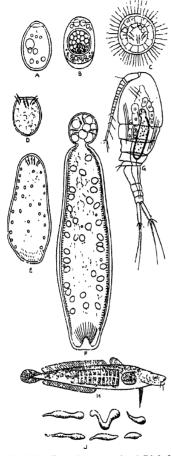


Fig. 267.—Evolutionary cycle of Diphyllobothrium latum. Drawn to different scales. (Partly after Brumpt.)

A, Egg of D. latum; B, hexacanth embryo; C, cliated onchosphere or coracidium; D, E, P, development of larva, or procercoid, in Cyclops; 0, procercoid in body-cavity of Cyclops; II, development of plerocercoids in fishes; J, plerocercoids of different shapes, ingested by man, dog, or cat.

barbel; in U.S.A. the pike, wall-eye and burbot. Reaching the stomach of the fish, the procercoid penetrates to the body cavity, and, after three to four days there, encysts as a plerocercoid or sparganum (6 mm.) in the muscular and connective tissues. Sucking, cephalic grooves, nervous and excretory systems are developed. It is then ingested by man with raw roe (caviare) or insufficiently cooked fish and the plerocercoid develops in five to six weeks into an adult Diphyllobothrium. Fresh-water fishes harbour other spargana which cannot be differentiated in this stage.

N.B. The process of "kippering" does not kill the plerocercoids, and ordinary smoking is ineffectual, but brine saturation is effective.

Pathogenesis and treatment.—Symptoms are usually trifling; there is early eosinophilia in a small percentage and even sometimes severe pernicious anæmia. Dried or alcoholic extracts of the worm cause destruction of red blood corpuscles, but not proportionately of the hæmoglobin, especially in patients

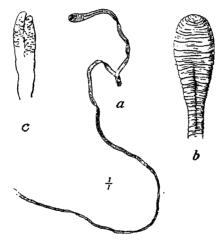


Fig. 268.—Diphyllobothrium mansoni plerocercoid, extracted from an abscess in a Masai. (After Sambon.)

a, Natural size; b, anterior extremity; c, posterior extremity.

previously subject to this anæmia; these extracts have no influence on normal blood or cryptic pernicious anæmia. The worms are expelled by filix mas, tetrachlorethylene, or oleoresin of aspidium. There are records of hundreds of feet of worms expelled after anthelmintic treatment without any appreciable symptoms, but Tarassov (1937), who experimentally infected himself, had marked abdominal pains and loss of weight.

Diphyllobothrium minus is a small variety which the Russians claim as a separate species. It has been found in Lake Baikal and has a similar life-history to that of D. latum. Its second intermediary hosts are various species of salmon and grayling which are eaten salted or frozen by Mongolian peoples.

DIPHYLLOBOTHRIUM MANSONI (Cobbold, 1882)

Synonym.—Dibothriocephalus mansoni.

Distribution.—Japan, China, East Africa, Australia and British Guiana. The adult form is found in the dog, wolf, fox, cat, leopard and tiger, and its plerocercoid in man, frogs and snakes.

Characters.—It resembles D, latum, is 6-10 m, long, and has a more delicate structure with a narrower and more ellipsoid egg than D, latum.

Its plerocercoid was named Sparganum mansoni by Cobbold. It was first found by Manson in 1882 at the autopsy of a Chinese. Since then 60 cases have been reported. The life history was worked out by Yoshida, and later by Okumura.

Life-history.—The adult stage occurs in the dog and other animals, the plerocercoid under natural conditions in the frog (Rana nigromaculata), or snake (Elaphe climacophora). The procercoid in Cyclops leuckarti shows the same stages as in D. latum.

Man is infected by accidentally swallowing a procereoid whilst drinking, thus becoming a second intermediary. The Chinese custom of applying raw split frogs to sores on the hands may be a chief portal of entry there. The sparganum in man measures 8–36 cm. by 0.1–12 nm. by 0.5–1.75 nm. thick (Fig. 268). Its body is flat and transversely wrinkled, with a longitudinal median groove. It is found in many parts of the body: kidneys and iliac fosse, pleural cavities, methra and subcutaneous tissues.

Ocular sparganosis in Tonquin (Casaux) is now becoming commoner. The plerocercoid gets into the orbit and causes pain, redness, ordema of the cyclids, lacrymation and ptosis. It has been found under the conjunctiva in Japan and China—probably also as a result of split-frog poultices, made from the tree frog (Rana limnocharis).

Treatment.—Intravenous neosalvarsan, 0·3-0·45 grm., is given, and repeated in four to five days. Tarsorrhaphy should be performed to preserve the cornea until the worms have been killed.

Spirometra mansonioides, or S. houghtoni, an aberrant form found in cats and

dogs in U.S.A., was differentiated by Mueller from D, mansoni by the poorly-developed bothria. The scolex measures 0.2- 0.5 mm, as against 0.4-0.8 mm.

S. mansonioides (Mueller, 1935) has now been found to be the parent form of Sparganum proliferum (Ijima, 1905) (Fig. 269). S. mansonioides is found in the intestine of the eat in the Southern United States, and is separable from D. latum and D. cordatum by the scolex, uterine characteristics and smaller size. Specimens vary from 20-60 cm. in length, but may attain 1 m. by 8 mm. Immature proglottides number 200-300.

The egg is pointed, 65 by 37 μ , with a conical operculum. The life history is as in D. latum.

The plerocercoids (sparganum) measure 3-12 mm. by 2.5 mm. (Fig. 269) and are contained in cysts, which are found in man in Japan and Florida. The body contains calcareous corpuseles. The cysts became disseminated throughout the body in the subcutaneous tissues, intramuscular fasciæ, walls of the alimentary

canal, mesentery, kidney, lung, heart and brain. The prognosis in man is grave. Similar pleroceroids have been reproduced in macaque monkeys.

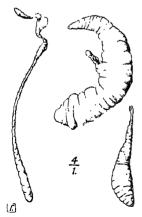


Fig. 269.—Different forms of Sparganum proliferum. (After ljima.)

CYCLOPHYLLIDEA

Tænia solium (Linn, 1758), "Pork tapeworm." (Fig. 270)

Distribution.—This is world-wide, co-extensive with the intermediary, the pig. The worm is unknown among Mohammedans and Jews, and is rare now in England, owing to meat inspection.

Characters.—It lives in the upper third of the small intestine. The name "solium" is derived from the resemblance of the rostellum to the conventional figure of the sun. It attains a length of 2-3 m.—exceptionally 8 m. The head is globular, quadrangular, 1 mm. in diameter, and the rostellum short and pigmented, with a double row of 20-50 hooklets (Fig. 270, 3). The four suckers project slightly and are circular, measuring 0.5 mm. in diameter. The anterior proglottides are small, broader than they are long, the more mature ones measuring 12 mm. by 6 mm. Each proglottis has a marginal genital pore with thick lips; its situation alternates irregularly between the right and left margins. The uterus is median with 7-10 stout diverticula (Fig. 271, A). The testes consist of 150-200 follicles, distributed throughout the dorsal plane. Proglottides number less than 1,000. Terminal ripe segments pass out in the fæces and have an independent movement which enables them to migrate outside the anus.

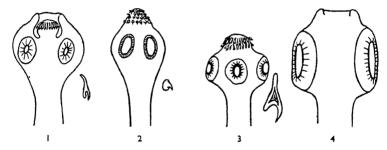


Fig. 270.—Heads of human cestodes, showing suckers and, when present, arrangement of hooklets. Diagrammatic.

1, Hymenolepis nana; 2, Dipylulium caninum; 3, Tania solium; 4, Tania saginata.

The egg measures $31-56 \mu$ in diameter, and is round with no operculum. It has two radially-striated shells, the inner formed by the embryo (thus differing from pseudophyllidea), and a vitelline membrane when it is in the segment which is lost in the fæces. Small numbers of eggs are found in the fæces when the segments break. They contain the six-hooked onchosphere (Pl. XXVI, 16).

Life-history.—Mature segments are detached and pass out with the fæces; they disintegrate and the eggs are set free and eaten by the intermediary host (the pig). Man is occasionally infected by cysticerci (see cysticercosis, p. 817), so are other primates, occasionally sheep or dogs. The onchosphere penetrates the gut wall and enters the bloodstream, settling in the muscles, where it loses its hooks, and becomes a cysticercus (5–20 mm.). Known as Cysticercus cellulosæ, it has a small, invaginated scolex and a neck, resembling a miniature adult tænia. Infected pork is popularly known as "measly pork."

In the alimentary canal of man, or other definitive host, the bladder of the cysticercus is absorbed by the gastric juices; the scolex and head are evaginated and then pass to the small intestine, where the scolex fixes itself to the gut wall and forms proglottides. In man, cysticerci are found in the tongue, neck, ribs, liver, heart, lungs, brain and eye, where they may persist for 20 years.

Epileptiform convulsions are frequently produced (p. 818). Larvæ may develop from viable eggs in the gut as an accidental infection, or auto-infection in persons infected with adult tænia. Clinically, this variety of bladder-worm is sometimes known as Cysticercus racemosus.

Pathogenesis.—*T. solium* usually produces no symptoms, but in debilitated persons or in children it may cause gastro-intestinal disturbances such as anorexia, vomiting, nervous symptoms and even anæmia. (For treatment, see p. 816.)

Tænia saginata (Goeze, 1782) "Beef Tapeworm." (Figs. 270, 271)

Distribution.—This is world-wide, wherever ox-meat is eaten; the worm is still fairly common in England, and is universal in Abyssinia, where multiple infections are common. It lives coiled up in the small intestine.

Characters.—T. saginata is whitish and semi-transparent, measuring 4-10 m., when fully adult it contains 2,000 segments. The scolex is pear-shaped, cubical; 1-2 mm. in diameter with four lateral suckers but no rostellum or hooks. The suckers and sucker-like organ at the apex are frequently pigmented. (Fig. 270, 4.)

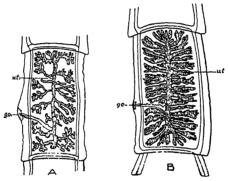


Fig. 271.—Segments of tapeworms. To show characteristic branching of uterus, as seen in mature segments.

A, Tuna solium. B, Tuna saginata. ut., Uterus; g.o., genital opening.
(After R. Blanchard, in Brumpt's "Précis de Parasitologie.")

The neck is long and half the width of the scolex. The older proglottides are elongated; gravid individuals are three to four times longer than they are broad. The genital pore is single, marginally placed at the hinder end of the proglottis, alternating regularly between the right and left margins. There are 20-35 lateral branches on each side of the uterus which may ramify. (Fig. 271, B.) The genital organs in the mature proglottis differ from those of *T. solium* in having about twice the number of testes (300-400) and in lacking the accessory ovarian lobe.

The egg is globular, 30-40 μ by 20-30 μ , with a double-shelled striated embryophore, which contains the onchosphere (Plate XXVI, 17). It is indistinguishable from that of T. solium.

Life-history.—Gravid proglottides emerge in fæces or pass to the exterior independently; they then creep into grass or herbage, where they disintegrate. When the eggs are eaten by the ox, the onchospheres are set free and pass into the small intestine, where they bore through the wall, and are carried to the muscles, especially the pterygoids and the fatty tissues round heart, diaphragm and tongue. Then cysticerci are formed, measuring 7.5-9 mm. by 5.5 mm. They

live for eight months in the ox and develop further in man, who constitutes the normal definitive host. The bladder is digested, and the liberated scolex, passing to the small intestine, affixes itself by suckers to the gut-wall. The cysts die at 48° C. Infected meat is known to inspectors as "measly beef." (Several varieties are described: T. africana, hominis, philippina, bremneri and confusa, have been attributed to new species, but are probably aberrant forms of T. saginata. Abnormal forms are common, such as T. lophosoma.)

Pathogenesis.—This worm occasionally causes abdominal pain, discomfort and anæmia. (For treatment, see p. 815.) Because of its large size the worm may be responsible for considerable disturbance in the normal functions of the digestive tract. The mass of an average specimen is about that of a liquid quart.

LARVAL FORMS OF TÆNIA IN MAN

The hydatid is the larva of *Echinococcus granulosus*; the adult lives in the intestine of dogs.

Cysticercus cellulosæ is the larva of T. solium (q.v.).

Cysticercus boris is the larva of T. saginata and has been reported in man on a few occasions.

Canurus cerebralis is the larval form of Tania (Multiceps) multiceps in the sheep. It is the size of a golf ball, and is diagnosed by percussing the sheep's head. The adult lives in the intestine of dogs, but is rare in man. The fourth case in man in S. Africa is described by Becker and Jacobson (1951). These cysts are far more common in sheep-rearing countries than has been realized. The focal symptoms are fainting attacks, hyperkinesis of the left arm and leg and staggering, but when the cysts discharge their contents they produce the psychological picture of toxic psychosis.

Ventriculography shows dilatation of the lateral ventricles. Headaches are common and there is severe papilledema. The hydatid complement-fixation test is positive. Two infections of the spinal cord causing spastic paraplegia have

been reported by Cruszi and Landells.

In M. multiceps the rostellum measures 200–250 μ ; the number of hooklets is 24–32; the size of the large hooklets 134–185 μ and that of the smaller ones 70–130 μ . M. glomeratus is normally found in gerbilles and has been found in the chest wall of a negro in North Nigeria. Its hooks and scoleces are distinctive.

ECHINOCOCCUS GRANULOSUS (Batsch, 1786)

Synonym.—Tænia echinococcus, or Hydatid.

Distribution.—The adult is a parasite of the dog, wolf, jackal, fox, arctic fox, monkey and kangaroo. It is common in Iceland, also in Esquimos, Australia, especially Victoria and Tasmania, New Zealand, and also in Arabia, Algeria, Tunis, Egypt, Abyssinia, Cape, Argentine and Uruguay, where the incidence in peons may be as high as 50 per cent. After ingestion of the egg by the intermediate mammal (sheep, ox, pig, camel, man) hydatids form, especially in the liver.

Characters. — E. granulosus is very small, 2.5-6 mm. long, with a pyriform scolex, 0.3 mm. in diameter, provided at the apex with a projecting rostellum, four suckers and two circular rows of hooks, varying in size and number. (Fig. 272.) The neck is short and thick; the proglottides usually four in number. The last one is the longest (2-3 mm.); only one is sexually mature and this contains 800 eggs. The genital apertures are marginal, one to each proglottis, in an alternating arrangement. The testes are spherical and numerous. The cirrus pouch is large and pear-shaped. The uterus is tubular and median, with short unbranched lateral diverticula. The adult is difficult to remove from the small

intestine of the dog without breaking its head. Eggs appear in the dog's faces. Sometimes the fourth segment also comes away. Man is probably not a suitable

intermediary.

The egg is ovoid, $32-38~\mu$ by $21-30~\mu$, and is double-shelled, the inner shell being thick. The onehosphere contains three pairs of embryonal hooklets. When swallowed, the shell is digested and the onehosphere escapes. After eight hours embryos can be found in the portal vein and liver, whence they are filtered out. The next filter is the lung, where a smaller number lodge. In three weeks the larval worm becomes vesicular and visible to the naked eye; in three months it attains a diameter of 5 cm. and within five weeks has doubled that size. The hydatid eyst wall is composed of a fibrous laminated layer formed by the host, a thick median striated layer secreted by the eyst, and an inner "germinal" layer from which the brood capsules and daughter eysts arise. There are two types of proliferation: (1) endogenous, (2) exogenous. In the former, proliferation is inwards towards the cyst-cavity: in the latter it is outwards. The varieties of hyatid are so striking that subspecies have been postulated, especially alreadar hydatid, which appears to have a limited geographical distribution.

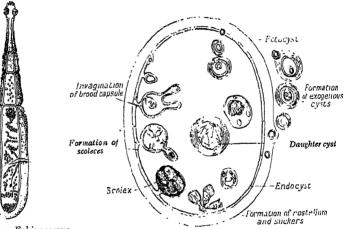


Fig. 272.—Rehinococcus granulosus. × 15. (After Leuckurt, in Brumpt's "Précis de Parasitologie.")

Fig. 273.--Schema of hydatid cyst. (After Blanchard.)

The brood capsules are formed from small nuclear masses of the parenchymatous germinal layer; later, they become vacuolated to form vesicles. Larval scoleces arise from a local thickening of the wall of the brood-capsule; the wall evaginates to form a protective cup for the growing scolex. Near the head-end the cuticle thickens and a circle of hooklets develops. The contractile part of the body of the scolex is capable of invaginating the head, so that in the typical resting position the scolex has the hooklets inside (Fig. 273). Free brood-capsules and free scoleces in the hydatid cyst cavity are known as "hydatid sand." In other cysts the brood capsules never produce scoleces and are known as acephalocysts.

Daughter-cysts may be produced by injury or by mechanical interference with the mother-cyst, inside which they arise from the detached germinal layer, and also from the brood-capsule cells; rarely by vesicular changes from the detached scoleces. In the liver the daughter-cysts are hile-stained. Intramuscular injection of scoleces causes formation of new cysts (Dévé and Dew) and this accounts for the dissemination of hydatid cysts throughout the body which sometimes occurs after operation.

Exogenous daughter-cysts in the omentum and bones are secondary, caused by herniation, or rupture of both germinal and laminated layers through weakened parts of the adventitia from intracystic pressure. By final exclusion of these herniations new cysts form.

Multilocular cysts occur in the lungs, and form solid tumours like sponges. They are produced by a double process: peripheral infiltration by the parasitic elements and central necrosis of the mass. Metastatic lesions of this variety are constant. This alveolar variety shows a peculiar geographical distinction in the Tyrol. Würtemberg, Russia and Siberia. Formerly, it was considered that the adult worm belonged to a different species, but this is incorrect. Surgical treatment is almost impossible, though partial hepatectomy has been attempted (Brins). Alveolar hydatid disease has now been reported from New Zealand, associated with ordinary hydatid cysts of the liver.

Dogs, foxes and jackals become infected by the adult worm through eating the organs, especially the offal, of sheep; the hydatid cyst wall is then digested and young tapeworms escape into the small intestine. Other naturally-infected animals are horse, camel, goat, monkeys, the Indian elephant, wild sheep, some antelopes, moose, tapir, zebra, kangaroo, mongoose, cat, leopard, squirrel, rabbit. Man is infected by close association with dog-eating from the same dish or kissing. The eggs are also disseminated by house-flies. Hydatids are common in children under ten. The symptoms vary according to the site of the cyst, and include toxemia, pyrexia, urticaria and multiple cutaneous eruptions. Tumours form in the liver and burst, disseminating secondary cysts in other organs, and these may suppurate and cause general peritonitis. In the brain the hydatid causes a cerebral tumour; in the liver, spleen and peritoneum it simulates malignant growth. In the lung it causes compression, and in the pleural cavity fluid exudate. In the kidney the mass resembles a hydronephrosis. It is also sometimes seen in the long bones, heart and orbit. The relative frequency of cysts in various organs of man is: liver, 57-76 per cent.; lungs, 3.8-14 per cent.; omentum, mesentery and peritoneum, 1.37-18.2 per cent.; pleura, 0.7-0.9 per cent.; skin, subcutaneous tissues and musculature, 0.7-9.1 per cent.; spleen, 1.2-9.1 per cent.; brain, 0.9-2 per cent.; spinal cord, 0.8-0.9 per cent.; kidneys, 1.6-6.1 per cent.; bone, 0.8-9.1 per cent.

The cyst wall shows an outer laminated chitinous layer and an inner germinal layer of small cells with muscular fibres, calcareous bodies and glycogen. The cyst contains a clear, watery fluid of specific gravity 1007–1015. containing albumin and a protein allied to casein, sodium chloride (0·5 per cent.), phosphates and sulphates of soda, sodium and calcium, succinates, traces of sugar and inosite, and an intracystic toxin allied to albumin. Hydatid fluid in the abdominal cavity produces shock, which is probably anaphylactic, and the escaped daughter cysts produce others. Hydatids are usually slow-growing, and cysts may be sterile. In man they tend to die and calcify, but may suppurate. Surgeons in Uruguay aspirate the fluid contents of the cyst. Following incision into the cyst itself the wall of the cyst is scraped out and the remaining parasite tissues treated with 1 per cent. formalin. Then the cavity is washed out with physiological saline, thus leaving no appreciable amount of formalin.

Diagnosis.—The hydatid appears as a cystic swelling which, if near the surface, produces fluctuation, "hydatid thrill"; if punctured by a syringe the scoleces and hooks are recognized. X-rays are helpful in hydatid cysts of lung, liver and when the long bones are involved. There are other aids to diagnosis.

(1) The precipitin test (Welch and Chapman):—equal parts of hydatid fluid and serum are mingled and incubated at 37° C.; if the fluid is infected a precipitate forms. (2) The complement-deviation reaction (Weinberg and Parvu) is generally accepted as reliable. It is performed by the Wassermann technique. Hydatid fluid (0.4 ml.) is mixed with an antigen made of scoleces macerated with alcohol (Fairley). (3) The Casoni, or intradermal, test is diagnostic in 90 per cent. (Kellaway and Dew). A few drops of the hydatid of a sheep are injected intradermally, and a reaction appears in ten minutes as a large wheal surrounded by erythema. It fades in an hour. A secondary reaction appears eight hours later; it is large and infiltrated by cedema. This test remains positive for years after the surgical removal of hydatid cysts.

Prophylaxis.—In endemic areas periodic deworming of dogs is effected by arecoline hydrobromide in the dosage of 4 mgm. per 100 pounds.

HYMENOLEPIS NANA (Siebold, 1852) (Fig. 274)

Synonym.—Tænia nana, H. murina, "Dwarf Tapeworm."

Distribution.—It is found in warm countries, Egypt, Sudan, Siam, India, Japan, South America (Brazil, Argentine, and especially Cuba), South Europe

(Portugal, Spain and Sicily, where it affects 10 per cent. of the children). It lives in the small intestine (Grassi bolieved it to be identical with *H. fraterna* of the rat) and parasitizes the Syrian hamster (*Cricetus auratus*) (Watson).

Characters.—H. nana is 5-45 mm. long and has 100-200 proglottides. The scolex measures 139-480 μ , is sub-globular with a well-developed rostellum, a single erown with 20-30 hooklets (14-18 μ), and four globular suckers (80-150 μ) (Fig. 270, 1). Theneck is long, the proglottides short anteriorly, but the posterior ones increase in size and are broader than they are long. The genital pores are marginal and placed near the anterior border. There are three testes. The vas deferens widens into the seminal vesicle, and the gravid uterus occupies an entire segment.

The egg is oval and globular, and there are 8-180 in each segment. It has two membranes, outer (vitelline), $40-46~\mu$, and inner, $20-30~\mu$ (Plate XXVI, 20). There is a conspicuous mammillate projection at each pole, enclosing an onchosphere with three pairs of hooklets.

The segments, when freed, are partially digested and the eggs, set free in the faces, are easily detected.

Life-history.—This worm forms an exception to other members of the group, in that it has no intermediate host; the larva enters the villus of the intestine to become a cercocystis (Villot). Its evolution was worked out in H. fraterna of the rat. In 40-70 hours after ingestion the scolex appears; in 80-90 hours the rostellum has hooklets and then passes into the lumen of the intestine attached to the epithelium of the villus by a short neck. The rapidity of development

varies greatly. Strobilization is rapid; the proglottides mature in ten to twelve days, and after thirty days eggs appear in the fæces.

Pathogenesis and treatment.—*H. nana* appears in large numbers—hundreds or thousands. It may produce no symptoms, but occasionally there is abdominal pain and diarrhea, rarely epileptiform convulsions, headache or strabismus.



Fig. 274.

Hymenolepis nana.

Magnified.

Nervous phenomena are due to the toxic products of the parasite. On account of its minute size, this worm is often overlooked. Diagnosis is made by finding the eggs in the fæces; care is needed because they are so transparent that they

may be missed.

 \check{H} . nana is not easy to dislodge by filix mas or oil of chenopodium; tetrachlorethylene (p. 817) is said to be more effective. Chloroquine has recently been advocated. Gentian violet is considered valuable, given in hard gelatin capsules; for an adult, gr. 1 three times daily for varying periods. One month should elapse before cure is assumed. The stools should then be examined by the D.F.C. method (p. 1083). An infected patient should not sleep in the same bed with another person.

HYMENOLEPIS DIMINUTA (Rudolphi, 1819)

Distribution.—This is a parasite of rats (Rattus decumanus, R. alexandrinus) and mice (Mus musculus and M. sylvaticus); it is found in man in Italy, South America, the Congo (common: Chesterman) and West Indies.

Characters.—It measures 20-60 cm. by 3.5 mm. The head is small and cuboidal with a small infundibulum. At the apex is a rudimentary rostellum with four small, unarmed suckers. The neck is shorter than the head. The proglottides increase in size as the tail is approached, and are broader than they are long.

The egg is circular or ovoid, measuring $60-80 \mu$. Its outer shell is yellowish and thickened, with indistinct radiations, and contains a hexacanth onchosphere.

Life-history.—The cysticerous stages occur in the body cavity of insects and fleas during their larval stages: Nosopsyllus (Ceratophyllus) fasciatus, Xenopsylla cheopis, Pulex irritans; in coleoptera and lepidoptera such as Asopia farinalis, Anisolabis annulipes, Akis spinosa and Scaurus striatus; also in South America, in Dermestes vulpinus, D. peruvianus, Ulosonia parvicornis and Embia argentina.

The rat becomes parasitized by eating infected fleas or other insects. The cysticercoids, when ingested by the definitive host, become adult in 17 days.

Treatment.—Oleoresin of aspidium is the drug of choice.

DIPYLIDIUM CANINUM (Linn., 1758)

Distribution.—This is a common parasite of the dog, cat and jackal. There are 100 records of its occurrence in man, especially in children in European countries.

Characters.—It lives in the small intestine, measuring 15–40 cm. by 2–3 mm. The scolex is small and globular, 0.55 mm. in diameter. The rostellum is retracted into the infundibulum and has three to four circles consisting of 28–30 hooklets (14–18 μ) of "rose-thorn" shape and four elliptical suckers (Fig. 270, 2). The proglottides are narrow and there are 200 or more of them. The segments measure 6–7 mm. by 2–3 mm. Two sets of genital apparatus are found in each segment; the genital pores are placed symmetrically at the lateral margins. The uterine cavities contain egg-nests, each consisting of 8–15 eggs. Mature proglottides leave the intestine. The egg is round, 35–40 μ across.

Life-history.—The cysticercoid stage is passed through in the dog-louse (Trichodectes canis), dogflea (Ctenocephālides canis) and human flea (Pulex irritans). Eggs are eaten by the larval flea, and the hexacanth embryo develops in the adipose tissue and muscles, being delayed until the adult stage is reached, first appearing as a procercoid and later as a cysticercoid larva. Infection of man is accidental, due to swallowing infected fleas.

Pathogenesis and treatment.—Usually there are no symptoms. Treatment is by filix mas, as for other forms of tania.

RAILLIETINA

R. CELEBENSIS, R. MADAGASCARIENSIS, R. QUITENSIS

These worms are found in Siam, British Guiana, Mauritius and Formosa, and the last has been reported by Léon in Ecuador. They are characterized by numerous hooklets of "coal-hammer" shape on the suckers and rostellum, and by unilateral genital pores on the proglottides. Bipe segments contain egg capsules. The ovoidal eggs possess conspicuously large hooklets. Usually they are parasites of birds, more rarely of rats. Their intermediary hosts are probably flies.

INERMICAPSIFER

This genus closely resembles the foregoing and cannot be distinguished from it by the ripe proglottides, but the head and the suckers are unarmed. In Central Africa members of this genus are found in hyracoidea (rock hyrax), and some four species in rodents. I. arricanthidis, a parasite normally of the field rat, was found by the Editor in a European child from Kenya. I. cubensis appears to be common in Cuba where 76 cases in man have been described by Kouri. Morphologically it appears to be identical with the foregoing. The life history of the species of this genus is unknown.

NEMATODES OR ROUNDWORMS

The sexes of these worms are separate. They are cylindrical, non-segmented and taper at both ends. They are white or yellow, sometimes semi-transparent and their eggs are characteristic (Plate XXVI).

Ascaris Lumbricoides (Linn., 1758)- "Round Worm" Distribution.—World-wide.

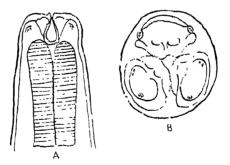


Fig. 275. - Head of Ascaris humbricoides; (a) ventral view; (b) anterior view, showing oral labia. (After Faust.)

Characters.—A. suitla of the pig is indistinguishable from A. lumbricoides whilst allied species are found in the cat, dog and horse. The worm inhabits the small intestine. The female measures 20–35 cm. by 3–6 mm.; the male 15–31 cm. by 2–4 mm. Both are pale yellow or brown, with whitish longitudinal lines,

round, tapering at both ends. The mouth is at the anterior end, guarded by thin lips with finely denticulated margins (Fig. 275). The anus is subterminal. In the female there are paired genital tubes, containing the uterus, receptaculum seminis, oviduct and ovary. Tubules and ducts attain a length of 12 cm. The total capacity of the genital tubules at one time has been estimated at 27 million eggs; the average output is 200,000. The male has the tail curved into a semicircle and has two rows of tactile papillæ and two chitinous spicules.

The egg (Plate XXVI, 7, 8, 9, 10) measures $50-70~\mu$ by $40-50~\mu$ and is elliptical, encased in a rough albuminous coat giving it a mamillated appearance. It is usually stained by fæcal pigments.

Life-history.—When the eggs are passed in the fæces, there is no segmentation or differentiated embryo. In water, or in moist earth, at 36-40° C, within two to four months the embryo is seen coiled up and moving inside the egg-shell. The

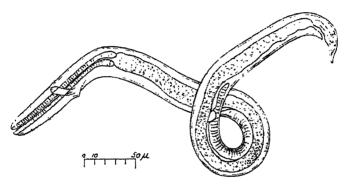


Fig. 276.—Larva of Ascaris lumbricoides recovered from the trachea of a rat eight days after ingestion of eggs. (After Brumpt's "Précis de Parasitologie.")

larva undergoes a moult before hatching and must be transformed into a secondstage larva of the "rhabditoid" type before it is infective. The embryo does not emerge from the egg until it is swallowed. The egg-shell is then softened by the gastric juice and hatches in the small intestine. The larva penetrates the mucous membrane, enters the blood via the heart and lungs, and reaches the alveoli where it has a "blood bath." Eventually it travels to the trachea. whence it is swallowed and reaches the small intestine. The whole process occupies ten to fourteen days. During this time the larva moults twice (once after five to six days and the second time after the tenth day). The larvæ measure 1.3-2 mm, on the tenth day (Fig. 276) and 1.75-2.37 mm, on the fifteenth (Stewart, Yoshida, Fülleborn, Brumpt, Mosler and Lutz). Larvæ may reach the intestine as early as the fifth day. The fourth ecdysis takes place in the intestine between the twenty-fifth and twenty-ninth days. In man the incubation period (to time of first oviposition) occupies a period of 60-75 days. The diameter of the migrating larvæ from the pulmonary capillaries to the terminal air spaces is considerably larger than that of the capillaries. Porcine ascaris larvæ are unable to complete their development in man: human ascaris behave similarly in the pig.

In the lungs the larvæ cause damage, hæmorrhage and toxic absorption. Eosinophil cells are found in the alveoli. The larvæ grow ten times longer whilst migrating through the lungs and feeding on the blood, but they are usually clear of larvæ in ten to twelve days. Aberrant migrations to thyroid, thymus

and spleen, occasionally to the brain and spinal cord, have been observed. Respiratory symptoms are noted 26 hours to four or five days after ingestion of eggs, and present the clinical picture of lobar pneumonia (ascaris pneumonia).



The adult worm may give rise during its wanderings to symptoms such as intestinal obstruction, general peritonitis, extraperitoneal abscess and even asphyxiation, when in the trachea. Exceptionally, viable eggs have been found in tubercle-like lesions in the mesentery. Children are occasionally infected by the ascaris of the cat and dog, Toxocara canis and T. cali. (For pathogenesis and treatment, see pp. 797, 799.)

Lagochilascuris minor has been recovered five times from abnormal foci in humans. The normal host is unknown.

PHYSALOPTERA CAUCASICA (v. Linstow, 1902)

Synonym.—P. mordens (Leiper, 1907).

Fig. 277.—Head of
Physaloptera
caucasica.
(After Leiper.)

Distribution.—Normal hosts are monkeys. In man it has been found in Central Africa, Portuguese East Africa, Uganda and Nyasaland. It lives in the cosphagus, stomach, small intestine, and occasionally in the liver.

Characters.—The female (2·4-10 cm. by 1·14-2·8 mm.) has a posterior end tapering to a sharp point, two ovaries, a single uterine tube, and a vulva in the anterior part of the body. The male (1·4-5 cm. by 0·7-1 mm.) has two lateral alæ on the tail, formed by expansion of the cuticle, four pairs of pedunculated papillæ—six pairs sessile—one unpaired postanal papilla, and two spicules of unequal length. In both sexes the mouth is guarded by two large lips, armed with two papillæ and rows of teeth, which serve to grip the mucous membrane. (Fig. 277.)

The egg (45 μ by 35 $\mu)$ has a double-contour, smooth, thick, colourless shell.

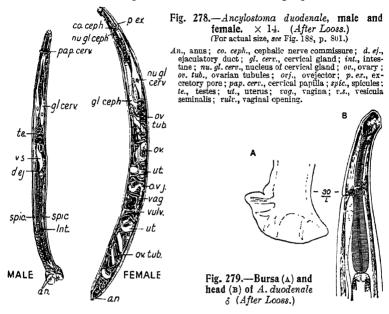
Life-history.—The life cycle is unknown; insects possibly act as intermediaries. The clinical symptoms are indeterminate. The worms live with heads embedded in the digestive tract from the cosophagus to the ileum-

ANOYLOSTOMA DUODENALE (Dubini, 1843) (Fig. 278)
"Old-World Hookworm," "Miner's Worm"

Distribution.—This worm was originally confined to Europe, but is now known in America, Asia, even Germany and England—wherever humidity and temperature are suitable (e.g., the Simplon tunnel, and the tin mines of Cornwall). It is very common in Egypt. It requires a temperature of 75° F. for development outside the body; this constitutes a limiting factor in distribution.

Characters.—Both sexes are cylindrical, white, grey, or reddish brown (from ingested blood). The female (1-1·3 cm. by 0·6 mm.) (Fig. 278), is cylindrical and slightly expanded posteriorly. The vagina is in the posterior third. The body cavity is occupied by the ovary and coiled uterine tubes packed with eggs. The maximum egg-output occurs fifteen to eighteen months after infection. The male (0·8-1·1 cm. by 0·4-0·5 mm.) has a copulatory bursa consisting of an umbrella-like expansion of the cuticle; the dorsal ray is divided towards the distal end into smaller rays, which again divide into three unequal portions (Fig. 279). There are two long delicate spicules. The genital papillæ are tactile, finger-like projections near the ano-genital opening. Owing to the situation of the genital openings in both sexes the worms in copulation assume a Y-shaped figure.

Two well-marked cephalic glands occupy the anterior third in both sexes and secrete an anticoagulating ferment. The mouth end is bent dorsally. The excretory pore is ventral, placed at the level of the cesophagus. The buccal



capsule is lined with chitin, and contains two pairs of sharp teeth on its ventral aspect (Fig. 280). The worm lives mostly in the jejunum, and to a lesser extent in the duodenum, but not in the ileum.

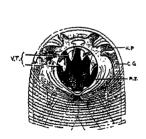


Fig. 280.—Head of A. duodenale, showing hook-like ventral teeth. × 50. (After Looss.)

C.G., Cephalic gland; H.P., head papillæ; P.T., pharyngeal teeth; V.T., ventral teeth.

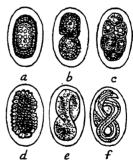


Fig. 281.—Developmental stages of the larva in eggs of A. duodenale. (a), (b) and (c) are seen in fresh stools; (d), (e) and (f) when the stool is stale. × 300. (After Loose.)

At autopsy 500-1,000 or more worms may be found. They have a life-span of four to seven years. The interval between active infection and final disappearance of eggs in the fæces may be 76 months.

The egg (60 μ by 40 μ) (Fig. 281) is elliptical, with a transparent shell. When fresh-laid, it contains 2–4 blastomeres (Plate XXVI, 14). For further details, see p. 1081.

Pathogenesis and treatment.—See pp. 803-807.

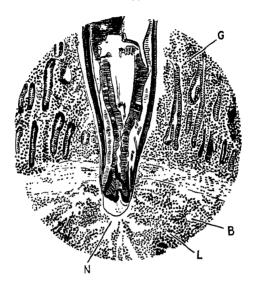


Fig. 282. Section through the duodenum showing the method of attachment of the ancylostome to the wall. (After Esmeja.)

it., blood-vessels; G., glands of Lieberkühn disrupted by the ancylostome; L., leucocyte infiltration; N., zone of necrosis.

Ancylostoma braziliense (Gomez, 1910)

Distribution.—It is found in dogs and eats in Brazil. In Ceylon it was described as A. ceylanicum from the civet eat.

Characters.—It is rarely found in the small intestine. Usually it is part of a mixed hookworm infection in man in India, Malaya, and Siam.—It is smaller than A. duodenale and the internal pair of ventral teeth are smaller than the corresponding teeth of that species.—The female is I cm. long and the male

8.5 mm. The rays in the copulatory bursa differ (Fig. 283) from those of A. duodenale, and are distinctive.

The egg is indistinguishable from that of A. duodenale.

Life-history.—This is the same as A. duodenale. Man is apparently an unsuitable host. The larva does not penetrate into the blood stream easily, but wanders under the skin, causing irritation ("larva migrans," p. 844), especially in South United States (Kirby-Smith, Dove and White, 1925-8).

Pathogenesis.—The signs and symptoms resemble those of A. duodenale.



Fig. 283.—Dorsal ray of Ancylostoma braziliense. (After Leiper.)

NECATOR AMERICANUS (Stiles, 1902) (Fig. 284)
"New-World Hookworm"

Distribution.—This is the only species of the genus. It is found in America, and is also common in West Africa, Ceylon, India, Pacific Islands, Malaya, the Philippines, and in pygmies from the Ituri Forest. Ninety per cent. of all hookworms from the tropics are of this species. It was probably introduced to America by slaves from Africa.

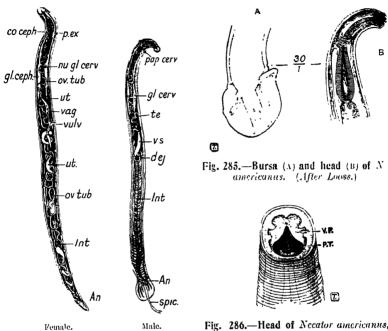


Fig. 284.—Neculor americanus. × 12.

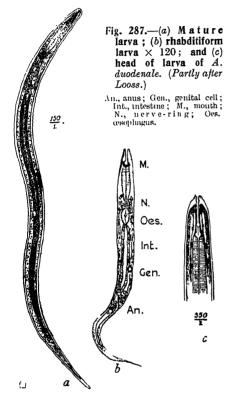
For legend see Fig. 278.

Fig. 286.—Head of Necator americanus, showing pharyngeal teeth (P.T.) and ventral plates (V.P.). × 50.

Characters.—It is found in the small intestine of man, and also of the gorilla, patas monkey, rhinoceros, pangolin and a rodent (Candu villosus). On the whole, N. americanus is a shorter and more slender worm than A. duodenale. The female (0.9–1.1 cm. by 0.4 mm.) has the vulva placed slightly in front of the middle of the body, so that it copulates at a Y-shaped angle, as in A. duodenale. The male (7–9 mm. by 0.3 mm.) has the copulatory bursa closed and blunt, and a short dorso-median lobe which appears as if divided. (Fig. 284.) The dorsal ray branches at the base into divergent arms with bipartite tips (tridigitate in A. duodenale). The base of the dorsal and dorso-lateral rays is short (Fig. 285). Two separate spicules unite to form a single terminal "fish-hook" barb. The living worms are greyish-yellow, at times reddish.

The sudden dorsal bend of the head, especially in the female, is distinctive. The buccal capsule is smaller than in A. duodenale, with an irregular border. In place of four hook-like teeth there is a ventral pair of cutting

The first pair of dorsal teeth are represented by chitinous plates (Fig. 286). plates. The outlet of the dorsal gland constitutes a "dorsal rib" or tooth which projects into the oral cavity. Deeply placed in the capsule are



one pair of dorsal and one pair of sub-median lancets.

The egg is slightly larger than that of A. duodenale (64-75 µ by 36-40 μ), but otherwise similar. The infective larva can be differentiated from that of S. stercoralis by the larger buccal vestibule and the intervening space between the esophagus and midgut. four eggs per grm. of fæces are reckoned to represent one female worm.

Life-history.—This is identical with that of A. duodenale.

SUMMARY OF LIFE-HISTORY OF HOOKWORMS (Fig. 287)

The eggs are deposited in the lumen of the intestine with two, four, or eight blastomeres. They must have a supply of oxygen to develop.

(1) The embryo moves about inside the shell and alters its shape, then escapes and gives rise to:-

(2) The rhabditiform larva which burrows into the fæces and feeds especially on bacteria. At first it has a double-bulbous œsophagus. (Fig. 287, b.) Feeding voraciously, it stores oil globules in its intestinal wall. It moults on the third day;

on the fifth the esophageal bulb disappears, and the larva becomes elongated and fully developed. It then moves away from the fæces into the earth, moults again and becomes :--

(3) The infective filariform, or third stage larva, with a well-developed mouth capsule, a simple muscular œsophagus and protective sheath, the walls of which are seen as two bright lines in the living specimen. It moves towards the oxygen supply, but cannot swim in water. Attracted by warmth, it is quiescent in the cold; it moves along a thin film of water as well as in the earth. Enabled by the sheath to withstand a certain degree of desiccation, it can live in warm damp soil under optimum conditions for two years. This is the infective stage. (Fig. 287, a.) On penetrating the skin of the host, the sheath is left behind, and the larva then enters the lymphatics, gains the blood-stream, and reaches the lungs on the third day. If pyogenic bacteria enter the skin with the larvæ an open lesion may develop, producing "ground itch." Breaking through the alveoli of the lungs, it enters the bronchioles, and travels via trachea and cosophagus to the stomach. During this migration the third moult takes place and the buccal capsule is formed. On arrival in the intestine on the seventh day it undergoes its fourth moult; the terminal buccal capsule is changed into the "provisional buccal capsule" with the mouth opening directed dorsally, as in the adult, but without teeth. On the fifteenth day the "provisional buccal capsule" is cast off, and it then assumes the adult form with adult buccal capsule and bursa in the male. In three to five weeks it becomes sexually mature, copulates and then produces fertile eggs. Females of A. duodenale lay about 2½ times as many eggs as do females of Necator americanus.

Cultivation of hookworm larvæ.—A small portion of fæces is rubbed over a Petri dish with warm water, making a uniform layer like pea-soup. Inside the cover is placed a circle of wet blotting paper. This is kept wet and incubated at 75° F. under a shade. If there is too much water the eggs will not develop. The larvæ climb up the sides of the dish on to the blotting paper where they can be studied.

Differentiation of third-stage larvæ: Table XII

	Necator.	Ancylostoma.
Oral capsule	Sharply defined ; visible dorsally and ventrally	Hardly visible; more marked dorsally than ventrally
Tail	Rather blunt	Pointed
Zone of closing cells	Leaves only small space between esophagus and intestine	Leaves considerable space

The striation of the sheath is indistinct in A. duodenale, but very distinct in A. braziliense. Rhabditiform ancylostome larvæ are similar to those of S. stercoralis, but are slightly more attenuated posteriorly and possess a much longer buccal vestibule. Infection (third stage) duodenale larvæ can also be differentiated from those of necator by the unequal esophageal shears which are unequal in thickness in Ancylostoma but equal in Necator.

ŒSOPHAGOSTOMUM APIOSTOMUM (Willach, 1891) (Fig. 288)

Distribution.—This worm has been found in 4 per cent. of prisoners in the jails of North Nigeria. It is a common parasite of the cæcum and colon of oldworld monkeys in Africa, the Philippines and China.

Characters.—When free or encysted under the mucous membrane of the large intestine it produces a condition like polyposis intestini.

The female (1 cm. by 0.325 mm.) terminates posteriorly in a sharp point and has a vulva in its anterior half. The male (0.8-1 cm. by 0.35 mm.) has a copulatory bursa with a dorsal ray bifurcating into branches and forming a horse-shoe-shaped structure, each limb giving off a short lateral horn near its base (Fig. 288, C).

The egg (60 μ by 40 μ) closely resembles that of ancylostoma, but is passed in an advanced stage of development.

Life-history.—The larvæ hatch from the eggs in the soil. When mature, they are unsheathed. The rhabditiform stage is swallowed, and passes through

the stomach and intestine. Then it invades the wall of the execum where it forms nodules. The immature worms break out into the lumen, attach themselves to mucosa and become adult.

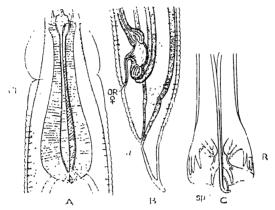


Fig. 288. -Æsophagostomum apiostomum (brumpti). (Partly after Railliet and Henry.)
 A, Head, showing cuticular expansion and oral vestibule. B, Tail of female. C, Tail of male, showing copulatory bursa.
 a., Anus; Cl., ventral cleft; OR, vaginal orifice; R., characteristic rays of bursa; 8p., spicule.

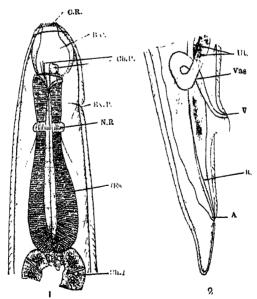


Fig. 289 .- Ternidens deminutus, female. (After Leiper.)

Anterior extremity.
 Posterior extremity.
 A., anus.
 B.O., buccal cavity.
 Ch.I., chyle intest.
 C.R., corona radiata.
 Ch.P., chitinous plates.
 N.R., nerve-ring.
 CEs., cesophagus.
 R., rectum Ut., aterus.
 Vag., vaginal opening.

Pathogenesis and treatment.—This worm produces dysenteric symptoms. It is apparently susceptible to phenothiazine, 3-7 grm., and tetrachlorethylene (see p. 539).

(Railliet and Henry, 1909)

Distribution.—This is a common parasite of monkeys (Cercopithecus callitrichus) and gorillas. The first case reported in man was in Brazil; the patient died of dysenteric symptoms and peritonitis (Thomas, 1910). It has also been reported in French Guiana (Joyeux) and in North Nigeria (Johnson, 1934).

Characters.—The morphology resembles that of O. apiostomum, but both sexes are larger and is distinguished by a corona radiata with 38 leaf-like spines. The eggs in the fæces resemble those of ancylostoma.

Life-history.—This is probably similar to that of O. a piostomum.

TERNIDENS DEMINUTUS (Railliet and Henry, 1905) (Fig. 289)

Distribution.—This strongylid nematode is relatively common in monkeys and baboons in Africa and Asia—Macaca sinicus, M. cynomolgus, Cercopithecus pugerythrus and Papio porcarius. In the small intestine of man it is not uncommonly found in Nyasaland, Portuguese East Africa, the Transvaal and Southern Rhodesia. It is not pathological, unless present in large numbers.

Characters.—The female (14-16 mm. by 0.73 mm.) has a genital orifice posterior and subterminal, and a short vagina opening into two uterine tubes. The male (9.5 mm. by 0.56 mm.) has the dorsal ray of the copulatory bursa dividing into two distal extremities, and each branch bifurcates again. (Fig. 290.)

The worm resembles a female ancylostome; its anterior extremity is not bent, and the mouth capsule is terminal, with a corona of setæ. At the base of the cup-like buccal capsule three serrated teeth guard the entrance to the cosophagus; this is characteristic of the genus Ternidens. (Fig. 289.)



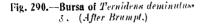




Fig. 291.—Egg of Ternidens deminutus. (After Blackie.)

The egg (84 μ by 40 $\mu)$ is delicate, transparent, and in an advanced stage of segmentation resembles that of an ancylostome. (Fig. 291.)

Life-history (Sandground).—The rhabditiform larva (0.3 mm.), with flagellar tail, hatches from the egg in soil, becomes sheathed, and the infective filariform larva (0.6-0.7 mm.) is formed. These can survive desiccation, reviving in water; thus they withstand drought. The larvæ fail to penetrate human skin. Carbon tetrachloride and tetrachlorethylene are effective in treatment.

Trichostrongylus colubriformis (Giles, 1892) (Fig. 290) and allied species

Distribution.—Normally, this is a parasite of the upper small intestine of the sheep and goat; it is not infrequently found in the duodenum and upper jejunum of man in agricultural districts of India, Central Africa, Egypt, Java, Australia, Japan, Korea and especially in Abadan (Persia), where 70 per cent. of inhabitants are infested (Stewart). It has been found by Bonne in Java in scrapings from the duodenum, where the adults live with head embedded in the mucosa. By flotation technique the eggs of this species can be found in the faces, together with ancylostomes (Lane), fairly frequently in India and Assam. Though rare in Europeans, the Editor once found them in a doctor and his wife from Kenya.

Characters.—The females (4-6.5 mm.) usually outnumber the males. They are very slender and pink, with an attenuated anterior extremity, and the vulva in the posterior quarter. The male (4-5 mm.) by 0.07 mm.) has a bilobed

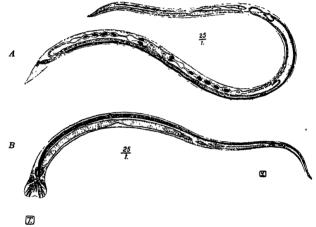


Fig. 292.—Trichostrongylus colubriformis. A, female; B, male. \times 25.

copulatory bursa and two spicules. These parasites are found, a third to a half buried in mucus. When scraped on to a slide they appear as delicate red streaks. When the slide is shaken in saline in a Petri dish they can be seen against a dark background. The adult worms are never found in fæces. The mouth is unarmed.

The egg (63 μ by 41 μ) is relatively large, oval, thin-shelled, and contains a morula when deposited. (Plate XXVI, 15.) It is apt to be mistaken for that of Ancylostoma duodenale, but is translucent and smaller.

Life-history.—The eggs hatch outside the body; the rhabditiform larve metamorphose into infective filariform in six days at $22-25^{\circ}$ C. The semi-filariform third-stage larve are very resistant to desiccation. These enter the body via the skin or mouth, undergoing two ecdyses, and follow the same course as ancylostomes.

Pathogenesis and treatment.—Usually there are no symptoms, but the worms may cause secondary anæmia. They are expelled by tetrachlorethylene (see p. 809).

An Eastern form has been separated in Japan (T. orientalis). T. probolurus (Railliet, 1896) is rarely seen in man; it is a natural infection of the gazelle and camel.

STRONGYLOIDES STERCORALIS (Bavay, 1876) (Fig. 292)

Distribution.—World-wide, especially in Brazil and Cochin-China. The parasitic form lives in the submucous tissue of the small intestine.

Characters.—Until recently it was thought that embryos were produced by parasitic, parthenogenetic female, in the absence of a male, but it is now claimed that a parasitic male (Kreis, 1932) exists, shorter and broader than the female. The œsophagus is said at first to be filariform, but American observers claim that it is double-bulbed and this feature renders their claims doubtful. (Fig. 293.) Later, two copulatory spicules and a gubernaculum are said to become apparen

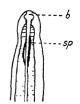


Fig. 293.—Strongy-loides stercoralis. (After Faust.) Anterior end of parasitic male. b., buccal spears.

spicules and a gubernaculum are said to become apparent and, when developed, the adult male resembles the free living form. (Fig. 294, 3.) This is a process of reversive metamorphosis, in which it loses the ability of penetrating tissues and remains a lumen parasite.

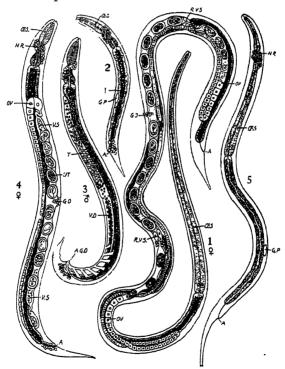


Fig. 294.—Life-history of Strongyloides stercoralis. × 30. (After Looss.)

1, Parasitic female; 2, rhabditiform embryo; 3, fully-grown male; 4, fully-grown female: 5, fully-developed filariform larva.

A., anus; A.G.O., combined anus and genital pore; G.O., genital opening; G.P., primitive genital organs; I., intestine; N.R., nerve-ring; C.S., cesophagus; O.V., ovary; R.V.S., rudimentary vesicula seminalis; T., testis; U.T., uterus; V.D., vas deferens; V.S., vesicula seminalis.

The female (2·5 mm. by 0·034 mm.) (Fig. 292, 1) tapers anteriorly and ends in a conical tail. The mouth has three small lips and leads to an esophagus occupying a quarter of the length of the body. The vulva lies in the posterior third. There is a prominent uterus containing 50 eggs (50–58 μ by 30–34 μ) which are laid in the lumen of the bowel in an advanced stage of development and may occasionally be found in the fæces. They hatch immediately to embryos (0·2–0·3 mm. by 0·013 mm.), which have a double-bulb esophagus, apt to be confused with the rhabditiform stage of Ancylostoma and Necator. (Figs. 294, 2 and 287.) They are passed active in fæces, and in 3–5 days are converted into free-living male and female forms, both of which have a rhabditiform, double-bulb muscular esophagus. The male is a free-living form (0·7 mm. by 0·035 mm.) (Fig. 294, 3), with the tail curved ventrally, two spicules and an accessory piece. The free-living form of the female measures 1 mm. by 0·05 mm. The vulva lies behind the middle of the body. The uterus contains thin-shelled eggs, measuring 70 μ by 40 μ (Fig. 294, 4).

Copulation between the sexes takes place in fæces. The rhabditoid larvæ produced are indistinguishable from those derived from the parasitic female. After 3-4 days they develop into post-feeding, mature filariform larvæ, which are the infective stage, and re-enter the definitive host via the skin or buccal mucosa, as in Ancylostoma or Necator, but may remain alive in the soil for many weeks. The distinguishing feature is that the cosophagus in strongyloides larvæ is half the length of the body (Fig. 294, 5); in Ancylostoma and Necator it occupies about a quarter. Filariform larvæ find their way into the small intestine and develop into female parasitic form. Under unsuitable climatic conditions, the sexual phase in the fæces may be omitted, and rhabditform embryos produced by the parasitic female may develop directly into filariform larvæ capable of infecting the definitive host. (Fig. 294, 5.)

SUMMARY OF LIFE-HISTORY OF S. stercoralis

Female parasitic intestinal form gives rise to eggs which, hatching in intestinal canal, give rise to:—

First rhabditiform larvæ in fæces which, at high atmospheric temperature give rise either to:—

Infective or to sexual forms which copulate, and females lay eggs from which emerge

Second rhabditiform larvæ which moult and give rise to:—

Filariform larvæ which enter man by penetrating the skin or through the mouth, and migrate through the lungs to the œsophagus. These develop in two weeks into:—

Parasitic female and (possibly) male in the small intestine. The latter is said to be almost identical with the free-living form; the females differ by being slender, filiform, with a cylindrical cosophagus extending through the anterior third of the body.

Diagnosis is easy when the active larvæ in the fæces are recognized by their morphology. They are often found in diarrhœic conditions, such as sprue. Duodenal intubation is the most certain means of diagnosis (Silva). When scanty the zinc sulphate flotation method of Faust may be used as it does not distort these larvæ.

Pathogenesis and treatment.—In large numbers this parasite produces irritation of the bowel and diarrhea, probably also abdominal pain and flatulence. Usually, it is found in men between 20 and 45 years old, in large

numbers, coiled up in the intestinal follicles. Infected individuals show supersensitization to the antigens of this parasite (Fülleborn). Itchy urticarial wheals are produced by the entry of or by rubbing into the skin dried extracts of strongyloides larvæ. In the recent war in the Far East this worm infection was associated with periodic urticarial eruptions within one foot of the anus and often on the trunk and thighs. The eruptions were sometimes petechial and sometimes linear like those of Larva migrans. They may be due to penetration of the skin by rhabtidiform larvæ or some may be allergic (as above). In one case the larvæ have been found within a lesion, when abundant in the fæces. A suggestion has been made that as the lesions are so characteristic a particular strain of Strongyloides must be involved. In transit through the lungs the young worms may be responsible for bronchopneumonia. Gentian violet, in enteric-coated

tablets, gr. 1, three times daily, up to a total of gr. 50 (3·3 grm.), acts as a parasiticide, if it reaches the parasitic female in sufficient concentration. The dosage is the same for children as for adults. In refractory cases 2·5 ml. of 1 per cent. aqueous solution of gentian violet may be introduced into the duodenum.

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The prophylaxis is the same as that for Ancylostoma.

Strongyloides fülleborni, a parasite of monkeys, recovered by Wallace and colleagues from an American soldier in the S.W. Pacific, is identified by prominent vulvar lips and narrowing behind the vulva in the free-living females. The prominent esophagus in the free-living stages is also characteristic.

ENTEROBIUS VERMICULARIS (Linn., 1758) (Fig. 295)
"Threadworm or Pinworm"

Synonym.—Oxyuris vermicularis.

Distribution.—World-wide (45 per cent. of school children are infected). It lives in the upper part of the large intestine, especially the cæcum. Occasionally it is found in the female genital organs, rarely in the ear and nose.

Characters.—This is the only nematode of man with a double-bulb cesophagus in the adult. It is small and white, its mouth surrounded by a cuticular expansion, and its skin transversely striated. The male is seldom seen, and does not migrate like the female. Much smaller than the female (2.5 mm.), its posterior third is curved spirally, and its caudal extremity blunt, with six sensory papillæ and a single spicule, $70 \, \mu$ (Fig. 295, c). The female (9-12 mm.) has a long pointed tail, the anus

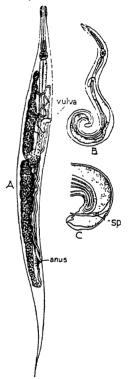


Fig. 295.—Enterobius vermicularis. × 12. (After Leuckart, in Brumpt's "Précis de Parasitologie.")

2 mm. from the posterior extremity, and a transverse, slit-like vulva in the anterior fourth of the hody. (Fig. 295, A.) The gravid female lays eggs in a stream of 10,000-15,000 in a few minutes and dies when egg-laying is completed.

The egg (50-54 μ by 20-27 μ) has a characteristic shape, flattened on one side, and is almost colourless, with a bean-shaped double-contour shell, which contains a more or less fully-formed embryo. (Plate XXVI, 19.)

Life-history.—There is no multiplication of worms inside the body. The egg shell is weakened by the intestinal juices and the larva breaks out of the shell. Soon afterwards it invades the glandular crypts and penetrates into the glands and stroma, where it coils up, causing some liquefaction of the tissues, but no cellular reaction.

According to Schüffner the length of life of E. vermicularis ranges from 37–93 days. As soon as the ovary becomes packed with eggs the female worm looses her hold on the intestinal wall and lies passive in the fæcal stream. The fertilized female migrates out of the anus to deposit her eggs in the perinaral skin and perinæum. The crawling of the gravid females produces intense pruritus. After few hours the embryo develops rapidly and attains a length of $140-150~\mu$. It is then ingested, generally as a result of deposits of fæces under the finger nails, conveyed to the mouth, and hatches in the digestive juices. Liberated larvæ after two months pass from the small into the large intestine, where they become mature. The whole cycle takes two weeks. Eggs can be inhaled through the nose from infected garments at some distance (Lentze), and embryonated eggs have been found in dust. Schüffner has described a process known as retrofection, in which infective larvæ re-enter the anus. The eggs require a six-hour exposure to air before they can hatch. In one-third of infected children the eggs are found in nail dirt.

Diagnosis.—This is difficult unless the worms are seen; they may be found outside the anus at night. Occasionally eggs may be found in the fæces. The mature worms penetrate the mucosa and encyst in the submucosa of the large intestine or appendix, causing inflammation. They are thought to be the exciting cause of appendicitis in 2 per cent. of cases, and are then found in the lumen. There is no marked eosinophilia. Nasal itching is common, and pruritus ani is produced when the ova are deposited in enormous numbers near the anus. The worms may enter the vulva and cause a mucoid discharge, restlessness and insomnia. Familial infections are common. The number of parasites infecting a host is determined by the number of eggs swallowed. The adult worms are phototactic and are attracted by the light of the electric bulb during sigmoido-scopy.

A cellophane sprayer "N.I.H. swab" (Fig. 296) has been devised, by which it is possible to obtain eggs by scraping the perineum (Hall). This device is much

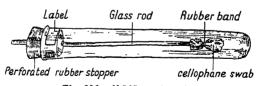


Fig. 296.—N.I.H. anal swab.

used in America. Enclosed in container, it is easily sent by post to be examined at leisure. The cellophane is mounted in water or N/10 NaOH on a slide, and covered with a coverslip. The "Scotch Tape" method in which the eggs adhere to the sticky surface is very popular.

Schüffner and Swellengrebel introduced the glass pestle method. A piece of thick-walled glass tubing about 1 cm. in diameter has a globe at one end, half of the surface of which is rough ground. The moistened globe is applied to the perianal skin with a rotary motion; the material is then dried on a slide and examined with cedarwood oil.

Treatment.—This is often difficult. Pruritus ani can be relieved by *Ung. hydrarg. ammon.* B.P. Quassia is also much used. After a salt-water enema, an infusion, 1 in 40 (10 ozs.), is injected slowly with the foot of the bed raised.

 β -naphthol, gr. 40, may be given in $\frac{1}{2}$ oz. castor oil or in cachets. Piperazine hydrate, in the form of syrup, at dose of $\frac{1}{6}$ gr. (11 mgm.) daily per year of life, is said to be most effective (White and Standen). The optimum dose level of 50–75 mgm./kg. daily.

Hexyl-resorcinol is especially used in America, given by enema, 1 in 2,000 solution, after evacuation with a soap enema. Two pints are given to an adult, and up to the limit of tolerance in children. This is repeated every three weeks, and in two-thirds of the cases negative swabs are subsequently obtained. The drug gives no better results by mouth (see p. 810). (Wright, Brady and Bozicevitch.)

Of the aniline dyes, gentian violet is prescribed in America in enteric-coated or water-soluble tablets, gr. ½-1, three times daily (gr. ½ for children) before meals for 10 days, or two periods of 8 days, each with a week's interval. Phenothiazine (phenovis) has an action on nematodes of the large intestine, and cures oxyuriasis when given in tablet or granular form. The dose for children under five is 0.5 grm., for older children 1 grm. for five days. Adults take 2 grm. daily for 7 days. A second course is sometimes necessary. The urine is stained red. Aplastic anæmia may be produced in children; therefore it is probably too dangerous for routine use.

Contraverm and reconox introduced by Eucker (1951) are similar preparations. Longer courses with smaller doses are most beneficial. A tablet is given the first day and two the second, to children of one to three; to those of three to eight three tablets a day or 0.6 grm. for eight to fifteen years, twice the same dosage to 1.2 grm. Ernst has given 4.2 grm. to adults in two days plus 0.16 grm. phenophthalein.

Egressin, a carbaminic acid, is recommended as an ideal vermicide in Switzerland (Sauer and Weissflug). Children two to twelve are given three separate doses of 1 grm. in two days with aperients (but not easter oil). Children take it best in cold pudding or cold coffee. Anal swabs showed that 95 per cent. ceased to pass eggs for 3–8 weeks. Itching and other symptoms disappeared after three doses.

Nyxolan-Hommel, aluminium 8-hydroxyquinoline sulphate, is given in tablets of 120 mgm. or in dragees thrice daily between meals for 5 days. Treatment is discontinued for 10 days and then repeated.

Terramycin acts on the gravid female, in single doses. The dose is below 5, 1 grm.; 5-10, 1.5 grm.; over 10, 2 grm. for 5-7 days (Loughlin and Rappaport, 1951).

Gammexane (Benzene hydrochloride or *Vermexan*) is used in Germany for adults, 150 mgm. daily, in three doses of 50 mgm. for three days. For children half that amount. This drug operates on the worms only.

Threadworms often disappear after a barium meal. The barium finds its way into every crevice of the intestine, and is able to reach the immature forms. Barium sulphate is given in 75 per cent. concentration in a six-ounce meal of umbrose; a second dose is taken 3 hours later and followed by calomel at night. The process is repeated next day. The dose for children is about three-quarters of that for adults.

Prophylaxis.—General measures must be taken. It is advisable to make the child sleep in cotton drawers and cotton gloves, to pare the finger nails, and to wash the hands after defæcation. TRICHURIS TRICHIURA (Linn., 1771)

Synonym.—Trichocephalus dispar "Whipworm" (Fig. 297).

Distribution.—World-wide, but more in the tropics than elsewhere. This worm is identical with a species found in pigs, and some monkeys. In many countries it is present in more than half the population.

Characters.—The male (30-45 mm.) has an anterior attenuated portion, containing the cellular cesophagus, which is half as long again as the thicker posterior portion. The caudal extremity is curved ventrally through 360 degrees, and there is a single spicule in the sheath, studded with spines. (Fig. 297, 3.)

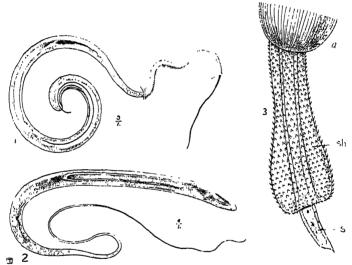


Fig. 297.—Trichuris trichiura. × 3. (After Brumpt.)

1, Male, partly embedded in the mucous membrane of the intestine; 2, female; 3, copulatory apparatus, greatly magnified.

a, Posterior extremity of body; s., spicule; sh., sheath.

The female (30-50 mm.) has an anterior attenuated portion, twice as long as the posterior half, which is occupied by a stout uterus, tightly packed with eggs. Females preponderate over males in a proportion of 466 to 1.

The egg ($50~\mu$ by 22 μ ; Plate XXVI, 18) is brown and has a characteristic barrel shape, and a single shell with a plug at each end. It contains an unsegmented embryo.

The worm is greyish-white or slightly pink and lives in the excum, where it maintains its position by transfixing a superficial fold of mucous membrane with its slender neck, and lying embedded in mucus between the intestinal villi.

Life-history.—Infection is spread chiefly by stale fæces. The eggs are unsegmented; embryonation takes at least 14 days, and the contained embryo develops very slowly, attaining its full size in 6-12 months. It can withstand

a low temperature owing to its thick shell, and remain latent for five years. Moisture is necessary and it cannot withstand desiccation. Development is direct. The embryo hatches only when the egg is swallowed: the egg-shell is digested by the intestinal juices, and the larva passes to the cæcum or large intestine, where it attaches itself to the mucosa and becomes adult.

Pathogenesis and treatment.—No special pathology is known, except that when in large numbers prolapse of the rectum may result (see p. 800), and the worm is of no great practical importance, save that the eggs should be recognized in the fæces. It is difficult to expel. Tetrachlorethylene and oil of chenopodium will remove a certain proportion (p. 810). In Mexico leche de hiqueron, the fresh latex of Ficus glabrata, is given; taken on an empty stomach in 2 oz. (60 ml.) doses, it gets rid of these worms. Unfortunately it rapidly ferments unless kept on ice. Hexylresorcinol in 1 in 2,000 solution has been advocated recently. The bowels are first cleansed by a soap and water enema, and two pints of the medicated enema for adults, less for children, is injected. One enema a week is necessary for a period of three weeks. A recent suggestion is 1.5 per cent. warm hydrogen peroxide solution, introduced into the intestine. Sandground has found that these worms are expelled after oral administration of emetine (gr. 1) in enseals. (For further details, see p. 800.)

CAPILLARIA HEPATICA (Bancroft, 1893)

Synonyms.—Trichocephalus hepaticus, Hepaticola hepatica.

This is closely allied to *T. trichiura*, and is normally a parasite of the liver of the rat, where the eggs are deposited in masses. They resemble those of the former, but the outer shell is distinctly pitted. It has a direct life cycle like that of *T. trichiura*. It has been found twice (Dive and MacArthur), on one occasion in a British soldier in India. Septic pneumonia, secondary to abscess of the liver, was caused by the adult worms. The eggs are present in liver substance but not in fæces. The second was reported by Brosius in Panama (1948) in a woman who lived on the livers of rodents which harbour the parasite. This infection was cured by oil of chenopodium.

TRICHINELLA SPIRALIS (Owen, 1935). (Fig. 298)

Distribution.—World-wide, formerly common in Germany, now found in U.S.A. (in 5 per cent. of the pigs of Boston; with modern digestive technique, it has been found in 18.6 per cent. of cadavers in Michigan), China, India, Syria (from eating wild pig), in Algeria and East Africa. Recent recrudescence in England and South Wales was ascribed to sausages. Pigs, wild boars, bears and rats are universally infected. Most animals, even lizards, are capable of infection in the laboratory, but birds are refractory. Infection takes place from pig to rat, and rat to rat, as sick rats are eaten by their fellows. Man is not a normal intermediary host.

Characters.—Trichinella is a white worm just visible to the naked eye. The male (1.6 mm. by 0.04 mm.) has a cloaca situated posteriorly between two caudal appendages and two pairs of papillæ. The female (3-4 mm. by 0.06 mm.) has a vulva in the anterior fifth, an ovary in the posterior half, and an anterior portion occupied by a coiled uterine tube. The anus is terminal.

The $egg(20~\mu$ in diameter) lies in the upper uterus, but the embryo soon breaks loose from the shell and lives free in the uterine cavity. The embryos are

voided into the lumen of the intestine and measure 100 μ by 6 $\mu.$

The worm inhabits the small intestine. The embryos emitted by the female migrate into the muscles where they encyst. The cysts are too small to be seen

at meat inspections unless they are completely calcified. The male dies soon after copulation, the female 5-6 weeks later after discharging hundreds of embryos.

Life-History.—When man consumes raw flesh infected with cysts of *T. spiralis* the cysts are digested out in the stomach and, after excysting in the duodenum, the larvæ invade the duodenal and jejunal mucosa and develop through four

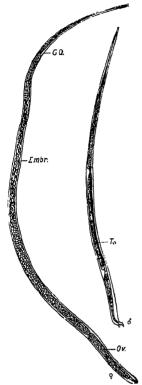


Fig. 298.—Trichinella spiralis, female and male. × 45. (After Brumpt.)

Embr., embryos; G.O., genital opening; Ov., ovary; T., testis.

ecdyses into adult males and females within 5-7 days. Whilst both adults and larvæ develop within the same host, two hosts are required to complete the life cycle. In Nature the infection is normally propagated by the black and brown rats, which are cannibalistic. Man usually acquires infection from eating inadequately cooked pork and also bear hams. The embryos, derived from the female, travelling via the lymphatics and venous channels, guided by instinct, pierce the coats of vessels and encyst in

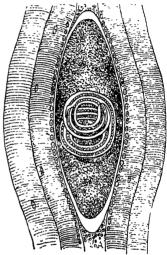


Fig. 299.—Encysted larva of Trichinella spiralis, filteen days after entering muscle. × 300. (After Claus, in Brumpt's "Précis de Parasitologie.")

striated muscles, especially the diaphragm, intercostal and laryngeal muscles and tendinous insertions in the neck and eye. (Fig. 299.) The cysts are oval, the cyst wall being formed by tissue reaction (Fig. 299). At first the adult worms may be lodged in the glandular crypts, but later the females burrow into the villi, and even into the mesenteric lymph glands.

Symptoms.—The symptomatology may be divided into three stages: (1) invasion (incubation), (2) migration of larvæ, and (3) encystation of larvæ and tissue repair. After an incubation period of 7-14 days the irritation of the duodenum and jejunum produces violent diarrhœa. There may be maculo-papular eruptions. In the second stage larvæ have been found in the corebrospinal fluid and their presence is not always accompanied by clinical symptoms (Evers), but some patients exhibit signs of meningitis: others encephalitis.

Symptoms at first may resemble those of cholera or dysentery with hyperpyrexia (T. 104°-106° F.). During migration of larvæ through the tissues there may be typhoidal symptoms with remittent temperature, a slow muttering delirium, muscular rheumatic pains, and difficulty in mastication, deglutition and respiration. "Splinter" nail hæmorrhages are characteristic. Three weeks later, when encystment in muscles has taken place, there is profound cachexia, due to absorption of toxins, cedema of the face, abdomen and legs, mental apathy, pruritus and skin eruptions. Death occurs in the sixth or seventh week from exhaustion or pulmonary complications. In recovery, the fever resolves, but the muscular pains persist. In Wolverhampton cases (1940) there were no severe gastrointestinal symptoms, but abdominal pains, edema of the eyelids and headache, suggesting influenza, and puffy face suggesting nephritis, with blood and albumin in the urine for a few days. Severe forms were described by Houston and Ross (1941) with hæmorrhages beneath the pleuræ and also in stomach and intestines, especially into the right psoas muscle. Myocarditis was one of the most serious complications. The mental attitude is identical with that of encephalitis. Splenomegaly was observed. Embryos were detected in the peripheral blood and could be demonstrated by mixing blood with dilute acetic acid and subsequent centrifugation. In the period of encystation there may be cachexia, toxic ædema or extreme delivdration. Nervous disorders include peripheral neuritis, defects of vision, delirium and encephalitis.

Diagnosis.—Eosinophilic leucocytosis appears soon after infection, and may be high; it decreases in the chronic stage, and is absent after nine years. Adult worms and embryos are found in the fæces. In the chronic rheumatoid stage, cysts can be recognized under the microscope in biopsy material. When calcified they may be demonstrated by X-rays. At autopsy, the pectoral muscles, diaphragm and laryngeal muscles (Gould) should be searched. In America, 50 grm. of muscle is digested by artificial gastric juice at autopsy. In the living subject a small portion of tissue obtained by biopsy can also be digested, and this is the best method of demonstrating cysts. They are found in U.S.A. in 20 per cent. of the population; in England in 1 per cent. (Van Someren). "Subclinical trichiniasis" is now recognized as a definite entity.

The precipitin test (Bachman), made with extracts of the parasite, becomes positive too late to be of value. An intradermal reaction may be produced by antigen prepared from artificially-infected rabbit muscle. This when injected causes both immediate and delayed reactions. American workers use 1 in 10,000 dilution of antigen in Coca's solution, which is more sensitive and gives positive

results two to three weeks after infection.

Prophylaxis.—Rats in pigsties must be destroyed, and pork, especially sausages, inspected carefully. Bear meat has been prohibited in U.S.A. and in Russia. Areas with the highest proportion of garbage disposal to swine give the highest trichiniasis rates in man.

Treatment.—No specific has yet been evolved. Injection of convalescent serum may control the toxic features. Good results have been observed after intravenous injection of 5 ml. of 10 per cent. calcium-gluconate (Lilly) during the migratory phase. Subcutaneous injection of carvasept (a preparation of thymol) in olive oil, or gum arabic, has given some promising results in America. A more hopeful method has been the use of the parathyroid—vitamin-D—calcium complex to secure calcification and death of the parasite within a shorter space of time. Parathyroid extract, 20–40 units every twelve hours for not more than ten days, is indicated, together with ergosterol and calcium salts (Van Someren). Sulphonamides and phenothiazine have had some success in experimental rats.

FILARIOIDEA

This group includes spirurate filiform nematodes adapted to inhabit the deeper tissues, such as the circulatory, lymphatic and connective tissue layers. Some insect intermediary is necessary to complete their development.

Wuchereria Bancrofti (Cobbold, 1877, Seurat, 1921). (Fig. 300)

Synonym.—Filaria bancrofti (Cobbold, 1877)

Distribution.—This is wide in tropical and subtropical countries, reaching north to S. Spain, in Europe and Charleston in U.S.A., and south to the Argentine, Transvaal, Brisbane in Australia, with isolated foci in North Central Africa and Egypt; in East Africa along the coast of Tanganyika, in the region of the great lakes, especially at Mwanza—Lake Victoria, and south to the Transvaal. It is common in West Indies, Brazil, South China, South India, Ceylon, Indonesia and in Melanesia, Solomon Islands, and New Guinea.

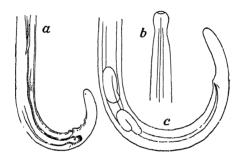


Fig. 300.—Parental forms of W. buncrofti. Magnified.

a, Tail of male; b, head and neck; c, tail of female.

Characters.—It is a thread-like white worm found in lymphatic vessels and glands. The sexes are coiled together, and can be separated with difficulty (Figs. 153, 154, p. 737). Buckley has shown that the cuticle is adorned with small cuticular bosses.

The male (4 cm. by 0-1 mm.) is coiled, with a corkscrew-like tail and two spicules, the larger of which measures 500 μ . The smaller (300 μ) is grooved on its ventral aspect. There is a short, thick proximal and a whip-like distal portion ending in a hook, and 15 pairs of minute sensory caudal papillæ. A saddle-shaped thickening of the cuticle on the posterior wall of the cloaca forms a shield, and there is an accessory piece peculiar to W. bancrofti (Fig. 300, a). There are 12 pairs of circumanal papillæ, of which eight are preanal and four postanal in position. There are also two pairs of large sessile papillae, and at the tail a solitary pair of minute size. The female (6.5-10 cm. by 0.2-0.28 mm.) has a tapering anterior end with a rounded swelling. There are sessile papillæ on the head and an oral aperture leading to a cylindrical osophagus. The mid-intestinal tube is one-third to one-fifth of the total diameter and opens into the rectum posteriorly. The caudal extremity is narrow and abruptly rounded (Fig. 300, c). The vulva is 0.8 mm. behind the anterior extremity. A swollen vagina (0.25 mm. in length) leads into the uterus, which divides into two tubuli, which are much coiled, occupying the greater portion of the body with a diameter three times that of the mid-intestine (Fig. 301). Two ovaries and ducts extend to within I mm. of the tail.

The eggs lie in the upper uterus enclosed in a chorionic membrane which becomes a sheath to the living embryos (microfilariæ) (Fig. 302). They are emitted by the viviparous female and travel via the lymphatics into the blood-stream, whence they are abstracted by various species of mosquito. Their size in the distal part of the uterus is 38 by 25 μ , but as they are pushed to the vagina they become more elongated. The microfilaria develop from an oval egg and measure at first 216 μ . The embryo often lies curled up in its shell which becomes lobed, resembling a Dutch twist, or "Pretzel."

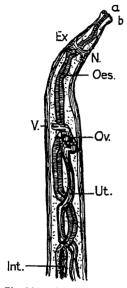


Fig. 301.—Diagram of head of W. bancrofti 9. × 50.
a., mouth; b., circumoral papillas; Ex., excretory pore; Int., Intestine; N., nerve-ring; Oes., cosophagus; Ov., oviduct; Ut., uterus; V., vulva.

Embryo (microfilaria) (280 μ by 7 μ).— Examined in the living state with a low power it appears structureless. With higher magnifications the entire embryo is seen to be enclosed in a sheath (structureless sac), which is longer than the enclosed embryo, so that this can move backwards and forwards, and the collapsed portion trails after the head or tail. In the middle third is some granular material, or primitive gut (Innenkörper). There is transverse striation of the muscular layer throughout. At one-seventh of the length from the head there is a break which denotes the nerve ring (n.r.) and one-fifth of the length there is a triangular V-shaped patch, demonstrated by light staining with dilute

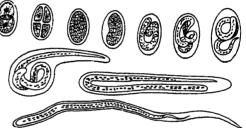


Fig. 302.—Evolution of sheathed microfilaria from ovum in uterus of parent worm. The later stages may occasionally take place after emission from vagina. (Partly after Penel.)

hæmatoxylin, known as "anterior V-spot," or the excretory pore and excretory cell (e.p. and e.c.). A short distance from the tail a second pore represents the anus, cloaca or terminal part of the primitive alimentary canal, and is known as the "posterior V-spot" (Fig. 307, 7). Deeply staining cells are known as genital cells (g.c.). When stained, the body of the embryo is seen to be composed of closely packed cells, and by focusing, when the movements of the living microfilaria have subsided, the head appears to be covered by a delicate prepuce. A short fang is from time to time shot out from the uncovered cephalic end and suddenly retracted (Fig. 157, p. 739).

Knott showed that microfilariæ pass with difficulty through the peripheral capillaries and that they are less active in day than in night blood. They are capable of movement and of transit from place to place (Drinker).

Periodicity.—Microfilariæ of W. bancrofti exhibit a nocturnal periodicity wherever they occur, in West Indies, South America, North, West and East Africa, China, Indonesia, New Guinea and Melanesia, i.e., they are present in peripheral blood in larger numbers during the night than during the day. The

maximum concentration is from 10 p.m. to 2 a.m. It appeared to Manson that this nocturnal periodicity was an adaptation to the habits of night-biting mosquitoes—Calex fatigans, C. pipiens and certain Anophelines—but the mechanism has never been satisfactorily explained. The numbers of the

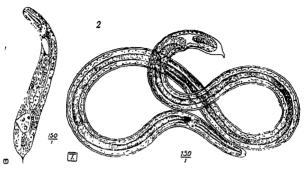


Fig. 303.—Stages of larval form of W. bancrofti, from thoracic muscles of Uulex fatigans. × 150. (After Looss.)

microfilarize are influenced by sleeping, and respond instantly to waking and bodily activity. By reversing the hours of sleeping and waking the periodicity is disturbed for three days and then reversed to diurnal periodicity. Recent observations on microfilarize of animals (Dirofilaria repens of dog, filaria of American crow and that of the Malayan monkey, Macaca speciosa) show that they also maintain nocturnal periodicity and are sensitive to light and darkness, and reversal is easily established. Periodicity is probably a quality inherent in

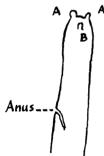


Fig. 304.—Larval filaria from proboscis sheath of Aëdes pseudoscutellaris. A.,terminal; B.,postunal papillæ. Length 1.4 mm. × 0.018 mm.

the microfilaria itself and persists unchanged in transfused blood (Hawking). (See also pp. 738–742.)

Life-history.—'The life-history was first worked out by Manson in Culex fatigans in China in 1878. one hour of entering the mosquito's stomach, the microfilarize cast the sheath's and bore through the stomach wall. O'Connor and Beatty showed that at the end of an infective feed the embryos collect at the anterior end of the stomach and then enter the anterior cylindrical portion of the midgut. Forward transportation is effected by reversed peristalsis until they are distributed over the whole of the cylinder. At the end of sixteen hours they form a writhing mass behind the valve which prevents their progress into the fore-The proboscis of the mosquito exerts positive chemotaxis upon microfilariæ. Therefore Culex fatigans or C. pipiens can abstract more embryos than would be present in a similar quantity of circulating blood. The mosquito abstracts 1 c.mm. of blood at each feed and,

in so doing, concentrates the embryos ten-fold. They next enter the thorax, where they lie between the muscular fibres (Fig. 305). Within two days they increase in girth, the "posterior V-spot" (or anal pore) enlarges, and the excretory vesicle becomes more prominent. By rapid nuclear proliferation the larval filaria now assumes a squat "sausage" form (Fig. 303, I), the tail shrinks and is then absorbed. Mouth and cesophagus are apparent from the fifth day onwards and the excretory pore is transformed into the anus. (Fig. 303, 2.)

When the larva is 0.5 mm. in length, a bulbar esophagus appears at the first and second fourths of the alimentary canal. Now, elongated and worm-like, the larva moves sluggishly about. Three caudal papillæ develop which function in progression and facilitate penetration of human skin (Fig. 304). About the tenth day (in favourable circumstances) the larval filaria, 1.4 mm. long, travels forward into the head, where it coils up and enters the proboscis sheath of the mosquito, but occasionally it may penetrate into the abdominal cavity and legs. Two or

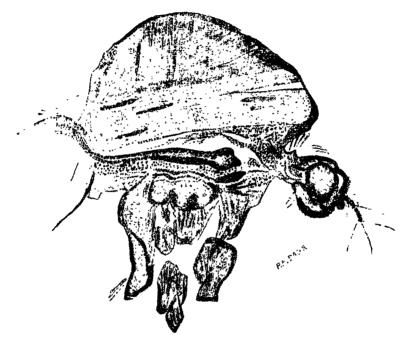


Fig. 305.—Section of thoracic muscles of Aëdes scutellaris (pseudoscutellaris): second day after feeding on filariated patient.

more ecdyses take place. At high temperatures and in moisture the complete cycle occupies ten to fourteen days, but it is retarded to six weeks by cold. Sometimes the larvæ die in the thoracic muscles and are enclosed in chitin, producing a curious mummy-like structure (Fig. 161, p. 744). When an infected mosquito bites man, the larvæ, attracted by warmth, break through the terminal portion of the proboscis sheath (Dutton's membrane), wriggle out on to the skin, which they penetrate near the seat of the puncture caused by the stylets of the mosquito (Fig. 306). Complete development of W. bancrofti has been observed in the following species of mosquitoes.

Culex fatigans (quinquefasciatus). West Indies, British Guiana, India, Philippines, S. China, Egypt, Queensland, Celebes, Indonesia.

- C. pipiens and C. pipiens var. pallens. China, Egypt.
- C. habilitator. St. Croix, West Indies.
- C. alis. Celebes.
- C. whitmorei. Celebes.

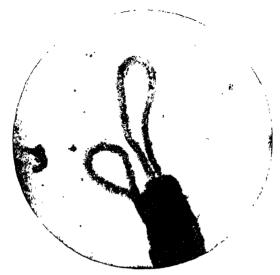


Fig. 306.—Larval W. pacifica emerging from proboscis of Aëdes pseudoscutelluris.

- C. rishnui. Celebes.
- C. vagans. China.
- C. annulirostris. Celebes.

Mansonioides annulifera. Southern India.

M. africanus and M. uniformis. Central Africa.

Aëdes togoi. Japan.

- A. chemulpænsis. Japan.
- A. ægypti and A. albopictus. Indo China.

Anopheles subpictus. India.

- A. nigerrimus. Southern India.
- A. hyrcanus var. sinensis. Japan, China, North-West India.
- A. funestus. Nigeria.
- A. gambiæ. West Africa.
- A. algeriensis. Tunis.
- A. amictus. Queensland, New Britain.
- A. albimanus. St. Croix, West Indies. A. albitarsis. Brazil.
- A. aconitus. Celebes.
- A. annularis. India.
- A. barbirostris. Dutch East Indies, Southern India and New Guinea.
- A. darlingi. British Guiana.
- A. punctulatus farauti. New Guinea, Solomon Islands, New Hebrides.
- A. stephensi. India.
- A. sundaicus. Sumatra.
- A. tessellatus. Maldive Islands.
- A. vagus. South India.

Some 22 species are listed in which partial development may occur.

In the human host the infective larvæ pass through the peripheral blood vessels to the lymphatics where they become mature in an estimated period of one year. Man is the only known definitive host.

WUCHERERIA PACIFICA.—Manson-Bahr, 1941

The Editor first suggested that the filaria found in Central and Southern Pacific might be a separate species. As far as can be ascertained, embryos (microfilariæ) are morphologically identical with those of W. bancrofti.

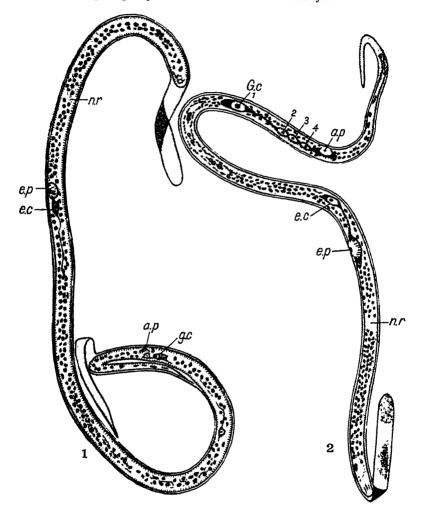


Fig. 307.—(1) Microfilaria bancrofti; (2) Microfilaria malayi. (From "A Comparative Study of Anatomy of Microfilaria Malayi and Bancrofti." Feng.)

n.r. = nerve ring ; e.p. = excretory pore ; e.c. = excretory cell ; g.c. 1. 2. 3. 4. = "genital cells"; a.p. = anal pore.

Microfilariæ in Polynesians (Fiji, Samoa, Tonga, Cook Islands) are non-periodic. In these islands as well as in Tokelau, Wallis, Ellice, Gilberts, Marquesas and those beyond "Buxton's line" (longitude 170° E.) they do not exhibit nocturnal

periodicity, but occur in equal numbers in the blood by day and night. Development of this filaria is confined to mosquitoes peculiar and indigenous to the S. Pacific Islands, Aedes scutellaris (pseudoscutellaris and A. s. polynesiensis (Marks)) in both of which maximum development occurs. The non-periodic microfilaria does not develop readily in C. fatigans, which is the optimum host for the nocturnal periodic form, W. bancrofti. A. s. pseudoscutellaris and A. s. polynesiensis are adapted to the coconut palm and have peculiar habitats (see p. 1046). The adult male 27 mm., female 58 mm., are smaller than those of W. bancrofti and the latter lacks the bulbous termination of the tail (Buckley) which characterizes W. bancrofti. In immigrants to Fiji nocturnal periodic microfilariæ (Solomon Islanders, New Hebrideans and Indians) retain their nocturnal periodicity, but, if members of these races are infected locally in Fiji. the microfilariæ found are non-periodic. In Europeans, Indians and in others contracting filariasis in Fiji the microfilarize also are non-periodic. This form of filaria produces enlargement of lymphatic glands, especially the epitrochlear. The adult filariæ are for the most part found in lymphatic glands. Chyluria and lymphuria are rare.

WUCHERERIA MALAYI (Brug, 1927) Rao and Maplestone, 1940

Distribution.—This is the common form in Malaya, Indonesia, Central India, Ceylon, South China, Korea, Indo-China and Koshima Island, Japan. (It has not been found in Africa, America, Australia or in the Pacific Islands.)

Characters.—Rao and Maplestone described the adults (1940) in Travancore; later (1941) Bonne and colleagues in Indonesia. They are practically identical with W. bancrofti in nearly all characters; the females are indistinguishable. The female measures 55 mm. in length by 160 μ . The vulva is situated 0.92 mm. from the anterior extremity. The caudal end is bluntly rounded. The male is 22–23 mm. in length by 88 μ in diameter. The posterior extremity has about three turns and the anus is 0.1 to 0.14 mm. from the tip of the tail. One pair of large papilla are just in front of the cloaca and one behind. There are also two smaller pairs. There is a small naviculate gubernaculum and two spicules which are unlike in size and structure. The longer is 0.34 to 0.36 mm.: the shorter 0.11 to 0.12 mm. in length. There are morphological differences in the microfilariæ and the mosquito intermediary is distinct—Mansonioides annulifera. Poynton proved that it is identical with a microfilaria of monkeys (Macaca irus) which is transmitted by the same mosquitoes.

The microfilaria of W. malayi was first discovered by Lichtenstein in Celebes,

and was studied further by Brug in 1927.

Microfilaria malayi has a nocturnal periodicity like that of $W.\ bancrofti$ (Brug, Poynton, Hodgkin, Gaillard, Liu, Feng and Yao). It measures 200-250 μ by 5-6 μ . Its chief points of distinction are the elongated nucleus at the tip of the tail and the absence of nuclei in the cephalic space. (Fig. 307, 2.)

The following table summarizes the main points of distinction between micro-

filaria malayi and microfilaria bancrofti:

TABLE XIII

MICROFILARIA MALAYI (Fig. 307, 2)

It is often found closely folded with head close to tail, and is irregularly disposed for, besides major curves, minor angulations are typical.

The nuclei are blurred and intermingled so that they cannot be easily counted.

MICROFILARIA BANCROFTI (Fig. 307, 7)

Usually seen lying with head and tail well separated, and commonly shows three or four major curves of graceful appearance.

The nuclei are well defined and spaced and can be easily counted

MICROFILARIA MALAYI

The tail tapers to a fine point, continued as a fine thread. There is typically one nucleus at the extremity of the tapered portion and two in the terminal thread.

The cephalic space is twice as long as broad.

The excretory pore and cell are separated.

The anal pore is a clear space about 40 μ from the tail end.

MICROFILARIA BANCROFTI

The tail tapers to a point and the terminal portion contains no nuclei.

The cephalic space is as long as it is broad.

The excretory pore and cell are close together and a thread of protoplasm runs posteriorly from the latter.

Treatment.—In W. malayi hetrazan clears the microfilariæ in the blood in the same doses as for W. bancrofti.

Life-history.—The most favoured mosquito intermediaries belong to the genus Mansonioides (p. 1043) which are crepuscular or nocturnal feeders. Development in the mosquito is similar to that of W. bancrofti, but more rapid, in 6-8½ days. In Celebes the intermediary is Anopheles barbirostris (Brug and Tesch). No development takes place in Culex fatigans (Gaillard). In China and Korea the appropriate species is A. hyrcanus var. sinensis; in Malaya, Mansonioides annulatus, M. annulifera, M. longipalpis and M. uniformis are equally suitable, being adapted to water plants, to the roots of which the larvæ adhere by their respiratory siphon. (Fig. 365, p. 1042.) In Koshima Island, Japan, development takes place in Aedes togoi (Sasa and Hayashi, 1953).

Relationship to W. bancrofti: the two species exist together, especially in South India and Malaya. The incidence of the latter is urban: that of W. malayi rural, depending on the presence of ponds with decaying matter and water plants. In towns W. bancrofti has a centripetal and W. malayi a centrifugal distribution. In South India Iyengar finds that, under natural conditions, W. bancrofti develops in Culex fatigans and Mansonioides annulifera. In Malaya, on the other hand, the species are Anopheles vagus and A. barbirostris. In S. Korea and in the Island of Quelpart, Senoo and Lincicome found it in 12 per cent.

Pathology.—Filariasis due to W. malayi produces especially elephantiasis of the legs (p. 751).

Prophylaxis.—Eradication of water plants necessary for the development of mansonioides has proved effective.

DIROFILARIA MAGALHÆSI (R. BLAND, 1895)

This filaria was discovered in Rio de Janeiro in 1887 in the left ventricle of the heart of a child. For a long time its classification and significance remained obscure. Then Faust and his colleagues (1941) reported a similar discovery in New Orleans. The specimen was a solitary male closely allied to, if not identical with, the dog heart worm, *Dirofilaria immitis*. This filaria may therefore sometimes occur as an accidental infection in man. The female is 155 mm.; the male 83 mm. in length.

MANSONELLA OZZARDI (Manson, 1897: Faust, 1930)

Synonym.—Filaria ozzardi.

Distribution.—West Indies, South America, Northern Provinces of Argentine (20–30 per cent. infected). Common in St. Vincent (West Indies) in aboriginal Indians (Caribs) of British Guiana, often together with *Dipetalonema perstans*. It was originally discovered by Manson in the blood of Carib Indians, and is now considered identical with *F. demarquayi*. The parental forms were discovered by Daniels in Demerara Indians and by Galgey in St. Lucia.

Characters.—The male, 3·2 cm., has a coiled tail and one spicule. The female (6·5–8·1 cm. by 0·21–0·25 mm.) has a vulva 0·76 mm. from the anterior extremity, and an anus 0·23 mm. from the tail. The caudal extremity has two prominent papille with a terminal thickened cuticle. The microfilaria (173–240 μ by 4–5 μ) is unsheathed and closely resembles that of D. perstuns, but has a sharp tail. (Fig. 152, b. p. 736.)

Life-history.—This was worked out by Buckley (1934) in St. Vincent, British West Indies (37.7 per cent. of the inhabitants infected). The intermediary insect is a midge, *Culicoides furens* (see p. 1048), a common pest; 27.5

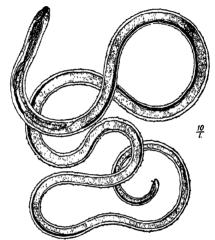


Fig. 308.—L. loa, male. × 10. (Partly after Looss.)

per cent. experimentally infected contained larval forms of this filaria. The ingested microfilariae migrate within twenty-four hours to the thorax; developmental stages are similar to those of *D. perstans*. Two eedyses occur; the largest—third stage—larvæ in the head measure 0.7 mm. Emergence from probossis takes place within eight days. *C. paransis* is possibly a vector in St. Vincent: *C. furens* in Antigua (O'Connor).

Pathology.—Montestruc (1949) thinks that it causes adeno-lymphocele. Treatment.—Microfilaria ozzardi is susceptible to hetrazan; 6 mgm. per kg.

LOALOA (Guyot, 1778) (Figs. 308, 309 and 173, p. 770.) "The eye-worm"

Distribution.—Widely distributed in West Africa from Sierra Leone southwards to Angola: mostly along courses of great rivers, Niger, Wellé, Congo (not in East Africa); especially common in Southern Nigeria and on Ogowé River, Cameroons. In Southern Sudan a closely allied form, L. papionis, is found in baboons (Papio cynocephalus). In the Cameroons one-third of one hundred and fifty monkeys investigated harboured a filarial infection indistinguishable from L. loa.

Characters.—The body is filiform, cylindrical, whitish and semi-transparent, with numerous round, smooth, translucent protuberances of the cuticle, 12–16 μ in diameter, and 9–11 μ above the surface. These chitinous bosses are more numerous in females. Their distribution is irregular. In the male they are

absent at the extremities; in the female they extend on the tail and also the cephalic end. The mouth is unarmed and destitute of papillæ; there is no distinct neck, but a shoulder 0·15 mm. from the mouth where there are two papillæ, one dorsal, the other ventral. The alimentary canal commences at a

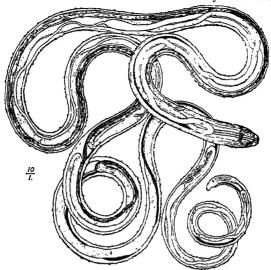


Fig. 309.—L. loa, female. × 10. (Partly after Looss.)

funnel-shaped mouth as a slender straight cesophagus, going on to an intestine $65~\mu$ wide, and a short attenuated rectum. The male (3–3·4 cm. \times 0·35–·43 mm.) has its maximum breadth anteriorly (Fig. 308); posteriorly it tapers to a tail, which is curved ventrally, with two lateral expansions of the cuticle (0·7 mm. \times 0·029 mm.) (Fig. 310.) In the middle, 0·08 mm. from the tail-tip is the opening of the ano-genital orifice with two unequal spicules (123–176 μ and 88–113 μ) surrounded by thick labia. There are four large globular, pedunculated papillæ, decreasing in size antero-posteriorly, and a fifth pair of small postanal papillæ.

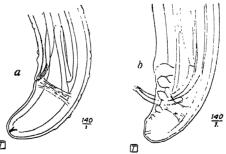


Fig. 310.—Posterior extremity of L. loa, (A) female, (B) male. (After Looss.)

The female (5–7 cm. \times 0·5 mm.) has a straight, attenuated, broadly rounded posterior extremity and a vulva 2·5 mm. from the anterior extremity placed on a small eminence. The vagina, 9 mm. long, branches off into two long uterine tubes extending through the length of the body. At the narrow end are the ovaries,

with eggs in all stages. (Figs. 309 and 310A.) Reproduction is ovoviviparous; the embryos develop within the egg envelope and uncoil themselves on expulsion from the vagina. When dead the adult worm often becomes cretified.

The embryo is known as microfilaria loa, or diurna, and is similar in size (298 $\mu \times 7.5 \mu$) and structure to microfilaria bancrofti. In fresh blood it may be impossible to distinguish them. In dried stained films (1) it assumes a stiff angular attitude, (2) the tail end is disposed in a series of sharp flexures, giving it a corkscrew appearance, with the extreme tip flexed, (3) the nuclei of the central column of cells of microfilaria loa is larger and less deeply stained. (4) The cephalic end of the column is more abruptly terminated. (Fig. 152, 2.)

Fig. 311.—Development of Loa loa in chrysops. × 30.

1, Larva, 24 hours old; 2, fourth day (length 390 \mu); 3, fifth day; 1, seventh day (length 1.5 mm.);

5, tenth day (length 2 mm., breadth 0.025 mm.).

(After A. and S. L. M. Connal, "Trans. Roy. Soc. Trop. Med.")

By special staining methods a large genital cell at the beginning of the posterior third constitutes a marked feature. Microfilaria loa takes up methylene blue (1 in 5000) in ten minutes. (Sharp, 1923.) In microfilaria bancrofti, absorption is much slower, but it shows up the excretory pore. Microfilaria loa may not be found in the peripheral blood until six or even seven years have elapsed from the primary infection. It is strictly diurnal (Chart 29, p. 770), from 8 a.m. to 8 p.m.—the reverse of microfilaria bancrofti. Inversion of periodicity takes place very gradually, as, for instance, when daily observations are made on a voyage round the world (Külz).

Life-history. (Fig. 311).—This proceeds in much the same manner as in W. bancrofti, but in the thoracic muscles, connective tissue and fat-body (Stevenson) of the bloodsucking "mangrove flies," Chrysops silacea and C. dimidiata (Fig. 378, p. 1050) in W. Africa and in the S. Sudan C. distinctivennis. On entering the stomach the embryo casts its sheath in three hours, and, piercing the stomach wall, enters the thoracic muscles and fat-body of the thorax, but principally that of the abdomen. Development is complete in ten days. In three days it becomes broad and torpedo-shaped; on the 4th and 5th days the squat-form is lengthened to 0.8-1 mm.; on the 6th, the corkscrew-like appearance is replaced by gentle curves. Then occurs the first ecdysis, and the sharp tail is replaced by a rounded trilobed extremity. By the 10th day it measures 2 mm. × 0.025 mm. and 3 ecdyses have occurred. Larvæ congregate in the head in large numbers, the majority at the root of the proboscis, and make their way on to the skin of the human host by piercing the proboscis sheath when the fly feeds (Fig. 312). It is capable of carrying infection for five days. In Calabar 3.5 per cent. of wild-caught chrysops are found naturally infected with Loa loa. When an infected fly feeds, large numbers of infective larvæ emerge and are deposited on the surface of the skin, from which they disappear rapidly, by burrowing in.

Development of the adult form in man occupies between 6-18 months. Fully adult worms may be found in almost all anatomical regions, but which are limited by connective tissue. In monkeys similar worms have been demonstrated moving along intermuscular septa and similar fascial planes. Many patients with loaiasis appear to have no microfilariæ in the blood, but in reality they are present in small inconstant numbers and can be detected by repeated examinations. Gordon suggests that microfilariæ may accumulate as a reservoir in the internal organs.

Pathogenesis and treatment (see pp. 771-774).

DIPETALONEMA PERSTANS (Manson, 1891; Railliet, Henry and Langeron 1912) (Fig. 313)

Synonyms.—Filaria perstans: Acanthocheilonema perstans.

Distribution. — Generally throughout Central Africa in man and chimpanzee. In Congo, Nigeria, Gold and Ivory Coasts, Sierra Leone, Northern Rhodesia, Uganda (90 per cent. infected); also in Venezuela, Trinidad. British and Dutch Guiana (but not in West Indies), Amazon Valley (Brazil) and Northern Argentine; possibly also in New Guinea. It is found in Europeans in Central Africa, commonly associated with microfilaria loa and bancrofti; and in British Guiana with microfilaria ozzardi. As individual



Fig. 312.—Development of L. loa in Chrysops silacea, showing several mature larvæ at tip of

(After A. and S. L. M. Connal, "Trans. Roy. Soc. Trop. Med. and Hyg.")

measurements differ so considerably, the South American form may well constitute a distinct species (Map VIII, p. 735). This microfilaria was described by Manson in 1891 and the adult form subsequently by Daniels in British Guiana.

Characters.—It has a long cylindrical, smooth body, and a simple, unarmed mouth. The tail in both sexes is characteristic: incurvated, with a chitinous covering at the extreme tip split into two minute appendages, giving a mitred appearance. (Fig. 313.) The male (4.5 cm. by 0.06 mm.) is smaller than the female. The head is 0.04 mm. in diameter, and the cloaca has four pairs of

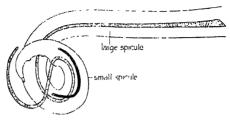


Fig. 313.—Tail of Dipetalonema perstans, showing two unequal spicules and papillae. (After Leiper.)

pre-anal and one pair of postanal papilla, and two unequal spicules (Fig. 313). The female (7–8 cm. by 0.12 mm.) has a club-shaped head 0.07 mm. in diameter, and a vulva situated 1.2 mm. from the head. The anus opens at the apex of a papilla in the concavity of the curve formed by the tail; its diameter is 0.02 mm. The microfilaria (200 μ by 4.5 μ) is unsheathed (Fig. 152, 5, p. 736). It possesses

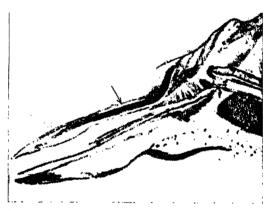


Fig. 314.—Larva of Dipetalonema perstans in proboscis of Culicoides austeni. (Dyce Sharp.)

in a remarkable degree the power of elongation and contraction. Therefore the measurements vary considerably. Brumpt et al. described long and short forms (90–110 μ by 4 μ). It is smaller than microfilaria bancrofti or loa and its caudal end is truncated and abruptly rounded. The tapering tail extends two-thirds of the entire length. The anterior "V-spot" is 30 μ from the anterior extremity. There is no marked tail spot, no central granular mass, and no cephalic prepuce. It moves freely in the blood, locomoting like the sheathless forms of microfilaria bancrofti. The microfilaria are found mostly in the heart, lungs, aorta and large vessels and spleen; rarely in the pancreas.

The embryos occur in equal numbers both by day and night, according to the self-inflicted experiment of Gönnert this embryo can persist in the recipient three years after blood transfusion.

Life-history.—Dyce Sharp described development in midges, Culicoides austeni and C. grahami (Fig. 314). It proceeds in the thoracic muscles, and, within six to nine days, the larval filariæ (0.7 mm.) are ripe for emergence from the proboscis. Before they emerge they cause a globular expansion of the labrum of Culicoides which then collapses and gives exit to larval filariæ; 7 per cent. of wild-caught midges are infected in the Cameroons. Although Henrard and Peel have thrown doubts on this, the validity of Dyce Sharp's work has now been confirmed in the Cameroons by Hopkins and Nicholas (1952).

Pathogenesis.—Adult worms occur singly in the mesentery, perirenal and retroperitoneal tissues and pericardium. This filaria may cause transient pains in the gall-bladder region. It is occasionally found in subcutaneous cysts. The Editor has made some observations which indicate that an allergic reaction, which resembles "Calabar swellings," may sometimes ensue. The incubation period is nine months to one year.

Treatment.—This microfilaris is killed by hetrazan, 5 mgm. per kg. (McGregor $et\ al.$).

DIPETALONEMA STREPTOCERCA (Macfie, 1922)

Synonym.—Agamofilaria streptocerca (Macfie and Corson, 1922: Stiles and Hassall, 1926).

Macfie described this sheathless microfilaria, found commonly in the corium of the skin, but not in the blood, of Gold Coast natives (22 out of 50 in Accra).



Fig. 315.—Dipetalonema streptocerca embryo, showing characteristic curvature of tail. \times 200. (Dyce Sharp.)

It probably has a wide distribution, especially in the Cameroons. The microfilaria (Fig. 315) is distinguished by the "walking-stick handle" of the tail extremity (Dyce Sharp). It is $215~\mu$ in length. The arrangement of nuclei in the head and the four prominent ones in the tail constitute an index of differentiation from the microfilaria of O. volvulus and D. perstans. Development takes place in Culicoides grahami and is similar to that described for D. perstans (Henrard and Peel, 1949).

Peel and Chardome found microfilariæ in the skin of 6 out of 11 chimpanzees (Pan paniscus and P. satyrus) in the Belgian Congo. Two adult female worms found in the connective tissue were closely similar to D. perstans. The microfilariæ of this species, D. vanhoofi, closely resemble those of the latter. The incubation period of D. streptocerca is 3-4 months. Wanson and others (1951) have shown that the microfilariæ are very susceptible to hetrazan and disappear from the skin in less than 48 hours.

Tetrapetalonema berghei n. sp. (Chardome and Peel, 1951)

This worm was found together with adults of *D. streptocerca* in the Belgian Congo at autopsy in man. The genus *Tetrapetalonema* was founded by Faust in 1935 and thus is the eighth species to be described.

It is a white nematode 60.9 mm. \cdot 0.271 mm. with almost imperceptible striations. Head is hemispherical and a relatively large genital opening is situated anteriorly. The uterus divides into two branches. Microfilariæ in all stages are visible in the uterus. There are several enlargements of the body at intervals. The caudal extremity narrows rapidly showing four excrescences. The tail is recurved. The microfilaria which is found in the skin resembles that of a small microfilaria perstans and measures 179 $\mu \times 3.55~\mu$. It may be that the adult form may turn out to be similar to D. perstans.

ONCHOCERCA VOLVULUS (Leuckart, 1893: Railliet and Henry, 1910) (Fig. 316)

Distribution.—West Africa, Sierra Leone to Angola, Congo, Katanga, North Kenya, Southern Sudan, Tanganyika, Mexico, Guatemala, Central America.

Characters.—The body is white and filiform, tapering at both ends. The head is rounded. The cuticle is marked by transverse ridges, and raised, with prominent angular and oblique thickenings, more distinct posteriorly. It is usually found in nodules, but can reproduce outside them (Van den Berghe). The male (2-4 cm. by 0.2 mm.) has a straight alimentary canal ending in a sub-



Fig. 316.—Caudal extremity of Onchocerca volvulus, & .

(After Brumpt.)

Sp., Spicules; An., Anus; p., Papille.

terminal anus. The tail ends in a slight spiral, and is bulbous at the tip. There are two pairs of pre-anal, two post-anal, an intermediate large papilla, and two unequal spicules (82 μ , 77 μ) protruding from the cloaca (Fig. 316); the former has a fluted end and the latter a narrow neck and knob. The female normally measures 60–70 cm. by 0.4 mm., but is often smaller, 35–40 cm. (Schäfer). The head is round and truncated (0.04 mm.), the vulva 0.85 mm. from the anterior extremity, and the tail curved. Cuticular striations are not so marked as in the male. It is ovoviviparous and the egg has a striated shell with a pointed process at each pole (like an orange wrapped in tissue paper)

measuring 30-50 μ in diameter. Usually males outnumber females by 2 to 1 (four males and two females in each tumour). (Brumpt separated a South American form as O. cacutiens, which is said to differ in the size and shape of the papillæ in the male and in the size of the spicules; but this is doubtful.)

The microfilariæ (300 μ by 8 μ) are sheathless and are found in the fluid of the cyst-cavity and in the surrounding skin: they are of two types, large and small (Blacklock). The body tapers from the last fifth and ends in a sharply-pointed, recurved tail (Fig. 152, 4, p. 736). In the anterior fifth is a marked anterior V-spot. The cephalic cone is thickened at the commencement of the nuclear column. This microfilaria is non-periodic; it is found in skin, in the femoral, inguinal and cervical lymph-glands and in the expressed juice of tumours, but rarely in blood (2 per cent.). It is also present in the skin of widely-separated portions of the body in apparently healthy natives, without producing any nodules or tumours. Microfilariæ are easily demonstrated in the skin by biopsy. They are often associated with eye symptoms, in the absence of tumours, and, by aid of the slit lamp, may be seen in the cornea, sometimes in association with massive elephantiasis of the legs (p. 778).

Life-history.—This was worked out by Blacklock, in Sierra Leone, where 45 per cent. of the inhabitants are infected. Development takes place in the "buffalo gnat," Simulium damnosum (Fig. 374, p. 1048) and in S. neavei in Kenya. the fly abstracts microfilariæ from the deeper layers of the skin near the nodule; They then enter the stomach, pierce its walls, and pass to the thoracic muscles

where they undergo further development. During growth one or more ecdyses take place. At the seventh day the larva measures $0.65\,\mathrm{mm}$. Development has been traced to the tenth day when the larva escapes from the proboscis; Simulium is a day-biting gnat (6 a.m.-6 p.m.) and 2.6 per cent. are naturally infected. They probably attract and then abstract microfilariæ by scraping the skin with their prestomal teeth.

In the South American form development is similar to that of the Central African, but occurs in Simulium avidum, S. ochraceum and S. mooseri, which are common in endemic areas in Guatemala. Developing larvæ are frequently found in the abdomen and Malpighian tubules of these flies. Two caudal papillæ are seen in fully developed larvæ, which measure 0.45-1.14 mm. In Guatemala 11 per cent. of simulium are naturally infected.

For pathogenesis and eye symptoms (keratitis punctata and interstitial

keratitis) see p. 779.

Dracunculus medinensis (Linn., 1758). "The Guinea-Worm"

Distribution.—This is a common parasite of man in India, Arabia, south-eastern regions of U.S.S.R., Korea, Sudan, Africa, especially Gold Coast; it has been imported into West Indies and South America, and is now endemic in Brazil and Guianas. Occurrence in the ox, horse, dog, wild-cat, jackal and leopard in Rhodesia is probably accidental. Dogs, monkeys and cats can be experimentally infected. In one endemic area—Bahia, Brazil—the parasite has died out as the result of extreme drought which dried up all the wells.



Fig. 317.—Dracunculus medinensis. Q One-third nat. size.

Characters.—The female is the thickness of a knitting needle and usually 2 feet in length (32.5 cm. $\times 1.5-1.7$ mm.; 90 cm. is probably exceptional, but 1 m. 20 cm. has been recorded by Ewart). It lives in connective tissues, and does not harm its host until about to produce its young, when it exhibits "geotropism," i.e., it is drawn towards earth, towards the limbs—to the fingers, if in the arms; to the scrotum or penis, if in the abdomen; to the breasts in the female, though 90 per cent. migrate to the legs and feet, especially behind the outer malleolus.

The body is cylindrical, white and smooth (Fig. 317). The tip of the tail is pointed, forming a blunt hook which was formerly thought to be used for holding firm in tissues, but this is not correct. The head is rounded, terminating in a thickened cuticle cap or "cephalic shield." The mouth is triangular, small and surrounded by six papillæ and an outer circle of four double papillæ. A lateral pair of cervical papillæ is situated behind the nerve ring (Fig. 318). There is a single-bulb cesophagus. The secretion from the head glands is very irritating, and blisters the skin of the host. The alimentary canal is small and is thrust to one side by the branched uterus. There is no definite anus. The vulva is difficult to see and has been only recently discovered as a very small tube in the centre of the worm. The whole worm is occupied by the double uterus packed with embryos (Fig. 319). There is a double overy at the posterior

extremity. When douched with water, waves of contraction force the uterine contents forward, and then the thickened cuticle gives way and the "cap" is blown off. The uterus is extruded up to a length of $\frac{1}{2}$ inch; this also bursts and the contained embryos are shed into the water. The worm dies when its

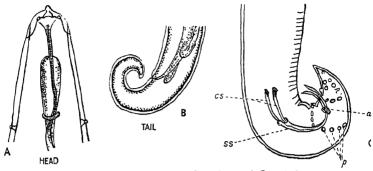


Fig. 318.—A, Anterior end and B, tail of D. medinensis. Q and, C, posterior end of d. \times 10. (After Faust.)

nervous system is destroyed. The sinus containing the dead worm easily becomes septic, but it may coil itself round tendons and, if pulled upon, breaks. It often becomes cretified and can then be demonstrated by X-rays.

The male has never been found in man, but was discovered by Moorthy (1937) in an experimental dog. It measures 1.2-2.9 cm., has sub-equal spicules (490-730 μ), and a gubernaculum (200 μ). The posterior end is coiled on itself



Fig. 319.—Transverse section of D. medinensis, showing contained embryo.
(After Leuckart.)

one or more times. There are ten pairs of caudal papillæ of which four are preanal and six postanal. After copulation it dies and is absorbed. It lives in between the muscles of the groin. Copulation probably takes place in the deeper tissues.

The embryo (Fig. 320) measures 500-750 μ by 17 μ and shows transverse striations of the cuticle. It is flattened, not cylindrical, with a long, slender tail, and a rounded head. The alimentary canal has a rudimentary anus and a bulbous esophagus. There are two glands at the root of the tail. In water the embryos cannot swim, but sink and coil up and release again, moving by

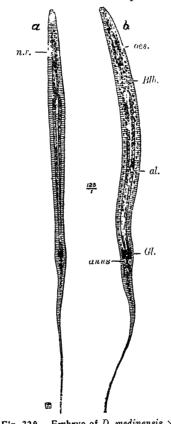


Fig. 320.—Embryo of D. medinensis \times 150.

a, Side view; b (after Looss), front view: oes., cesophagus; Blb., bulb, al., alimentary canal; Gl., glands: n.r., nerve ring

side-to-side lashing of the tail and tadpole-like movement of the body. Abnormal embryos, with prominences on the dorsal and ventral caudal surfaces, are not uncommon (Moorthy), but do not survive long.

Life-history.—In water they live for six days; in muddy water or moist earth two to three weeks. If slowly desiccated, they can be revived by water. They are swallowed by Cyclops when coiled up in rounded masses (cyclops has a very small mouth). The efficient intermediaries are Cyclops quadricornis, or allied species (C. strenuus, C. viridis, C. coronatus, C. bicuspidatus, Mesocyclops leuckarti and M. hyalinus). In S. Nigeria the species is Thermocyclops nigerianus. Jerky movements of the embryo attract cyclops as a trout is attracted by a fly. As many as twenty may be found in one crustacean, but usually they die out when there are more than four. The pointed tail penetrates the gut wall; they then migrate into the body cavity and feed on the ovary or testos of the cyclops. There is no growth in size, but two to three ecdyses take place. The tail is absorbed and they become cylindrical and the posterior extremity trilobed. Development takes four to six weeks. When 1 mm. in length they acquire a simple muscular cesophagus (Fig. 321) and the tail is truncated. This distinguishes the infective stage.

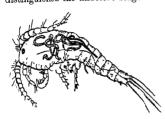


Fig. 321.—Larvæ of D. medinensis in body-cavity of cyclops.
(After R. P. Strong.)

Cyclops is swallowed by man; in the gastric juice the body of the cyclops is dissolved and the larvæ become active and burst out. Further stages in man are unknown. The adult worm takes one year to develop. In some Indian villages 38-6 per cent. of the cyclops are infected (Liston); in Dahomey an even higher percentage has been reported (Chatton).

The guinea-worm is limited to certain parts of the tropics by its need for suitable species of cyclops, and by the nature of the water supply. There is

a regular rhythm of infection during one or two months of the year—January and February on the Gold Coast—during and at the end of the dry season. An infected cyclops is not active, but lies prostrate at the bottom of wells. Therefore in the dry season the buckets bring up many more infected cyclops and the liability of natives to infection is increased. Infection is easily controlled. Any filtration of water, even through a handkerchief, will remove the crustaceans. The native practice of bathing guinea-worm ulcers at the side of wells should be prohibited. Wells should be provided with a parapet and they should be sealed, and pumps erected.

Fedchenko is credited with the discovery of the transmission of the guineaworm, but probably Manson was the original observer (1895). Leiper believes that the stages figured by the former are those of Cucullanus, not of D. medinensis.

For pathogenesis and treatment see pp. 784-788.

III. Medical Entomology

ARACHNIDÆ

ORDER ACARINA (Ticks and Mites) Sarcoptes scabiei (Linn. 1758). Itch-Mite (Fig. 322)

Morphologically similar species are found on domestic animals, foxes, wolves, and llama.

Scabies.—Scabies is widespread in the tropics, especially in North Africa.

The female $(0\cdot3\cdot0\cdot4$ mm.) of S. scabiei is bigger than the male $(0\cdot2$ mm.). The sexes may be further distinguished by the epimera of the second pair of hind-legs which unite near the sexual orifice in the male; in the female they are free. There are suckers (ambulacra) on the much reduced legs of the female, and on the first, second and fourth legs of the male. The gravid female lays eggs in a burrow in the skin. The greater part of the surface of the female is covered

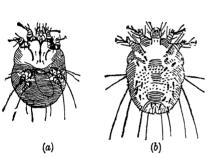


Fig. 322.—Sarcoptes scabiei: (a) ventral aspect with egg. × 35. (After Canestrini.) (b) dorsal view. × 40. (After Brumpt.)

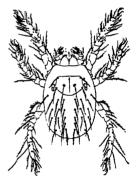


Fig. 323.—Larva of Trombicula autumnalis, the "harvest mite." × 50. (After Hirst.)

with fine transverse folds. The upper surface bears a number of specialized spines and conical scales.

The oval eggs measure $150~\mu$ by $100~\mu$; in three to five days they give rise to larve and nymphs which live like adults, and pass through four stages in three weeks. Finally the nymphs moult, become sexually mature, and pair off on the surface of the skin. The average life of the adult is four to five weeks.

Sarcoptic mange (Animal scabies).—This is sometimes contracted by contact with dogs, cats and cattle infested with their own biological races of sarcoptes. They may be distinguished from human scabies by the distribution of papules and vesicles on the arms, shoulders, trunks and thighs, and by the absence of burrows on the hands. Sarcoptic mange is much more amenable than scabies to treatment with sulphur compounds.

Treatment and prevention of scabies.—Scabies is unlikely to be spread by blankets, but may be passed on in underclothes. Lack of washing facilities aid in its dissemination. "Norwegian scabies" is a severe type accompanied by profuse crusting and pustulation, as is often encountered in lepers. In West Africa it is often known as "craw-craw." The objection to sulphur ointments, which formerly were extensively used in treatment, is liability to sulphur dermatitis, but sulphur lather tablets (18 per cent. sulphur) are an improvement.

As the lather dries, a thin film is deposited over the body.

Mitigal and Sudermo are less irritating compounds of sulphur which are rubbed on the affected areas on three consecutive evenings, and left to dry. Kathiclan, a Danish preparation, is active and was used in the British Navy. Marcussen's ointment is Ung. pot. polysulph. B.P.C. Proscabin (Kissmeyer, 1937) and Ascabiol consist of a lotion of equal parts of benzyl benzoate, industrial spirit and soft soap. An aqueous solution is found by Mellanby to be more effective, though apt to cause dermatitis. The treatment is effected in forty-five minutes, without damage to the skin, and is inexpensive. The whole body is anointed with soft soap and the patient soaks in a warm bath (100° F.) for ten minutes. Using a brush of pigs' bristles, the body is brushed with 11 oz. of the lotion. A second course is taken next day. The introduction of this method was an important advance, particularly for large numbers; it is rapid and simple. Rotenone lotion (B.D.H.) is the active principle of derris, and is a non-oily. mucilaginous preparation containing 2 per cent. of rotenone. It is applied twice daily for two days and is effective in mild cases. Tetraethylthiuram mono-sulphide (I.C.I.) in 5 per cent. solution is rubbed over the body, with the exception of the face and head, twice daily and does not cause dermatitis. It is cheap, clean and effective. The latest method of treatment consists of per cent. gammexane in vanishing cream. One application is said to suffice.

Demodex folliculorum var. hominis (Simon, 1842) (Fig. 324)

This mite is found in sebaceous glands and hair follicles, and is universally distributed. Usually it produces no symptoms, but it may give rise to dermatitis.



Fig. 324.—Demodex (After Brumpt.)

and some species in animals to mange. A minute degenerate acarid, 0.3-0.4 mm. in length, it is not found in infants. Its structure is primitive. The head is provided with elongated rostrum. The female lays heartshaped eggs (60-80 μ by 40-50 μ), from which hexaped larvæ develop. All the stages of development are passed within the follicles. The mature parasites migrate over the skin. To demonstrate them, sebum, expressed from the mouth of the sebaceous glands, or comedones, is examined with a drop of xylol. This parasite may give rise to a chronic dry crythema with follicular scaling. An ointment containing beta-naphthol and sublimed sulphur is said to be specific.

Pediculoides and Mites.—Pediculoides ventricosus, folliculorum. × 100. found in cotton and cereals, usually feeds on caterpillars. In dock labourers and others handling cotton and crops it gives rise to dermatitis. The abdomen of the pregnant female is swollen with eggs like that of a miniature

chigger; in it the eggs hatch and the young complete their development. Treatment is by carbolic lotion. (See p. 691.)

Tyroglyphus mites are found in cheese, flour and sugar, and cause copra itch or grocer's itch. The dermatitis may also be partially due to food sensitization.

LINGUATULIDÆ

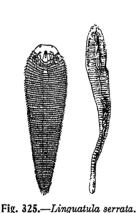
The linguatulids, pentastomes or "tongue worms," are degenerate arachnids with an annulated hody, which gives them a rough resemblance to tape-worms.

LINGUATULA SERRATA (Frohlich, 1789) (Fig. 325) This is found in Southern Germany, Switzerland and Brazil.

This linguatula (Fig. 325) in its adult state inhabits the nasal cavities of dogs, wolves, and foxes; rarely of sheep or goats. The larvæ are met with frequently in the mesenteric glands of domestic animals, as well as in rabbits and hares, and were found by Zenker in 4.6 per cent. of human livers, but appear to cause no symptoms. In Brazil it has been recorded as an intestinal parasite. The infection seems to be acquired through eating raw vegetables contaminated by nasal secretions of dogs.

Characters.—The body of the parasite is somewhat pear-shaped, flattened, and transversely striated with about 90 rings; the mouth is roughly quadrangular and surrounded by hooks. The intestine is simple. The male is white, 18-20 mm. long, and measures 3 mm. broad anteriorly, 0.5 mm. posteriorly. The female, 8-10 cm. in length, is grey, but may be brown when packed with eggs; anteriorly she measures 8-10 mm. broad: posteriorly 2 mm.

The eggs are ovoid, and 90 μ in length by 70 μ in breadth. They contain ripe embryos when deposited by the female, and pass out with nasal mucus to become



(After Brumpt.)

Fig. 326.—Porocephalus armillatus. Nat. size. (After Sambon.)

1, Larval form (x 6); 2, mature form (nat. size).

attached to grass and other herbs; they are then ingested by the definitive host, penetrate the intestinal coats, and enter the viscera, the liver, lung, mesenteric glands, kidney, etc. The larva, having grown to 5-6 mm. in length, encysts, and is ingested by various carnivora, then escapes from the cyst, falls into the peritoneal cavity and even into the intestinal lumen, and in this manner reaches the adult stage in the nasal cavities of the same host.

Porocephalus armillatus (Wyman, 1848)

Synonym.—Armillifer armillatus (Fig. 326).

P. armillatus occasionally infects humans, especially negroes in Central Africa. It has been recorded from Java (Salm), Manila, Sumatra, and China.

Characters.—The adult parasite is found in pythons and other snakes; the nymphal form in the lion, mandrill, giraffe and African hedgehog. The arachnid is vermiform, vellowish and translucent. The anterior part is cylindrical, the posterior tapering into a blunt-pointed cone. In the male there are 17-in the female 18-22—prominent opaque rings (each 1-2 mm.). The male is 3-5 cm.

long, the female 9–12 cm. There is no clear separation between the cephalothorax and the abdomen. The mouth opening is capped by two prominent papillæ on the ventral surface, lipped by a chitinous ring. On either side are two protractile chitinous rings; the anus is terminal. The genital orifice of the male lies at the anterior end of the abdomen; that of the female opens in the middle of the ventral surface of the caudal cone. The female is oviparous. The eggs are broadly elliptical, double-shelled, and measure 108 μ by 80 μ .

The nymph lies coiled within the cyst, with its ventral surface corresponding to the convexity of the curve. In shape and structure it resembles the adult.

Calcification may take place in the liver and other organs.

The life-history of P. armillatus is similar to that of L. scrrata. There is no doubt about the gravity of a heavy infection, when the parasites are migrating in the intermediary host. Broden and Rodhain have found them in 33 out of

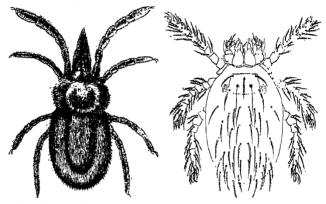


Fig. 327.—Trombicula akamushi: fullgrown imago. × 35. (After Mizajima and Okumura.)

Fig. 328.—Larva of Trombicula akamushi. × 80. (After Hirst, "Journ. Economic Biol.")

133 post-mortems on the Belgian Congo; a large number were within the lumen of the small intestine, and many encysted in the lungs. Manuwa has (1935) reported an acute and fatal case in Nigeria. At autopsy numerous nymphs were found in radicles of the portal vein and attached to the mesentery. When cretified, the parasites may be demonstrated by skiagraphy as in Low's case (1936). Otherwise, diagnosis during life is impossible. In oriental regions P. armillatus is replaced by P. monthformis, which is also parasitic in pythons. It is more slender and has more rings. Two cases of infestation with P. crotali of the rattlesnake have been reported in U.S.A.

TROMBIDIIDÆ

These are small, orange-red, "velvet mites," predaceous on their own kind, and on other insects and on plants. The larvæ resemble minute larval ticks, but bear bristles on their back. The harvest-mite (Fig. 323), the larva of Trombicula autumnalis, is small (0.5 mm.), just visible to the naked eye; it hatches out from eggs laid on the ground. These mites are normally parasitic on moles and hares; they live a few days on man, causing intense itching points with purpuric blotches. Inunction with dibutyl phthalate (see p. 241) is now used as preventive and cure.

Eutrombicula batatas (Trombidium irritans), the "chigger mite" of America is widely distributed, from Long Island and California to Mexico. The larvæ attach themselves to the skin, but do not burrow in; secondary infection is produced by scratching. Local application of kerosene or 95 per cent. alcohol is curative. Dusting the clothes with flowers of sulphur is preventive. In Mexico Neoschoengastia nunezi produces an irritating inpetiginous rash. Similar mites occur all over the world: the adult stages, known as "money spiders," are non-parasitic. Schöngastia indica is the commonest mite parasite of rats of Java and it is believed to transmit rickettsiæ to them. Of medical interest are Trombicula akamushi, T. schüffneri, T. deliensis and T. hirsti, "Kedani mites," the larval stages (microtrombidium) of which carry rickettsia of "scrub typhus" (Figs. 327, 328). The hexapod larvæ live on the ears of the field-vole (Microtus) and the house-rat of Formosa (R. rattus rufescens), whilst other rodents may act as reservoirs. The mites attack men working in fields, producing a local necrotic ulcer. In Malaya workers engaged in weeding palm plantations: in the Dutch East Indies labourers clearing jungle are especially affected. These mites do not suck blood, but when firmly attached, inject a digestive fluid which is a proteolytic ferment. This fluid dissolves the tissues so that the resulting liquid may be utilized. The skin of the host becomes hardened, and a tube (stylostome) is formed in which the mite lies and where it continues to imbibe the fluid until it is replete. Then it retreats and drops to the ground. The reaction of this digestive fluid causes the bite to itch. The tube represents a reaction of the host to the secretions of the mite.

Although T. akamushi and T. deliensis are the only proved vectors of Rickettsia akamushi some 100 new species have been discovered since 1940. The chief reservoirs of infection of the mite-borne as well as of the tick-borne fevers of the typhus group are believed to be these arthropod vectors. The vertebrate hosts are now regarded as being merely transitory reservoirs. In Malacca tomb bats,

Taphozous melanopogon, are found infested with T. deliensis.

The adult form (Trombicula) lives in soil, and measures 0.9 mm. by 0.5 mm. It is pale grey or red, with rudimentary eyes, four pairs of legs, the anterior pair stout, situated on the anterior part of the cephalothorax parallel to the pedipalps. On the ventral surface are two pairs of suckers close to the genital orifice and anus. The Trombicula feed on insect eggs. They deposit their own eggs in late spring or early autumn in loose top soil under leaves in damp places. The hexapod larvæ hatch in three weeks (measuring 0.32-0.43 mm. in length). They remain attached to their mammalian host, feeding for 3-4 days. They then drop to the ground and in 5-6 days moult and produce an eight-legged nymph. The infection of rickettsiæ by Trombicula may be hereditary. The larva (microtrombidium, or leptotrombicula) (0.4 mm. by 0.25 mm.) resembles that of the harvest mite, with its stout legs, pedipalpi and body, including the legs, covered with minute plumose hairs. The cephalothorax bears a conspicuous pair of red The nymph has a peculiar figure-of-eight shape, with abdominal constriction, and measures 0.65 mm. In due season it moults and becomes adult. Tetranychus molestissimus is a mite which may cause "larva migrans" (see p. 844). This belongs to a group known as "red spiders," which infest vegetation and are well known as the "Bicho Colorado" of South America. Persons employed in picking hops often complain of the itching produced by it.

For critical review of acari as transmitting agents, see S. Finnegan (1946),

B.M. (Nat. Hist.) Economic Series, No. 16.

IXODOIDEA (TICKS)

Ticks are cosmopolitan, and important carriers of disease. These large, bloodsucking Acarina are larger editions of mites. With the exception of Argas and Ornithodorus, they rarely attack man voluntarily in their adult stage. The

females are invariably larger than the males. The shell is often highly ornamented, and has four pairs of segmented legs, and a single spiracle on each side between the third and fourth legs. The males never gorge themselves on blood to the same extent as the females. When they are gorged the posterior end expands. Ticks are divided into ARGASIDÆ (soft), and IXODIDÆ (hard). In the former there is no shield, the mouth parts are not visible from above, and there are no festoons. All lay shiny, spherical eggs in enormous numbers—up to 5.000. The genital pore is situated in the middle line on the ventral surface. not far behind the capitulum. The excretory organs, or Malpighian glands. open into the hind gut and the coxal glands, which open on the front coxe. These hatch into hexapod larvæ, which become octopod nymphs, three series of which usually develop before the adult stage is reached. All are endowed with a phenomenal capacity for fasting—some for 4-5 years.

Argasidæ live apart from their host, in burrows or crevices, and have the habits of a bug. Adult ixodidæ attach themselves to the host, and drop off when gorged; and after fertilization the male dies. In some species-Margaropus the metamorphosis from larva to nymph, and from nymph to adult takes place on the same host; in others-Hæmaphysalis-the tick drops off before

each moult, to find a new host three times in its life.

ARGASIDÆ (SOFT TICKS)

GENUS ORNITHODORUS contains 20-30 species Ornithodorus moubata (Murray 1877, Fig. 32, facing p. 183)

This tick is widely distributed in Central Africa. The body is rounded and mammillated and the legs tuberculated. The integument is greenish-brown. hard and leathery, marked above and below with symmetrically-arranged grooves, and numerous hard, shiny trabeculations. The carapace contains no eves." The females (12-14 mm.) are larger than the males (8 mm. by 7 mm.) and moult frequently. The habits resemble those of the bed-bug, and it lives in native huts, thatched roofs, and cracks in floors and walls, emerging at night to suck the blood of man and beast, and in doing so it injects also an anticoagulant and analgesic. O. moubata is found in burrows excavated by ant-eaters and occupied by porcupines far from human habitations in Kenya and there they breed in large numbers (Heisch). It feeds slowly and cannot abstract much blood, except from a sleeping host. It is important as a vector of relapsing fever (Spirochæta duttoni). Spirochætes pass through the gut wall, and small infective forms arise in the body cavity and settle in various tissues, especially the ovaries, but not in the salivary glands. Spirochætal infection is transmitted in a hereditary manner, and the organisms have been found in the eggs. If the tick is allowed to feed for a few minutes, infection is not contracted, but fluid which contains the spirochætes is passed via the anus and coxal glands at the base of the second pair of legs, soon after the tick begins to feed. After about 10 minutes the whole surface of the tick becomes wet and the organisms enter the skin through the bite-wound. Eggs are laid in batches of 50-100 and the fertility of the female is favoured by liberal feeding. They hatch in 20 days and the larval stage is practically absent. On the thirteenth day the eggshell splits, and about the same time the skin of the contained larva splits also, and an eight-legged nymph emerges, throwing off simultaneously both egg-shell and larval skin. There are several nymph stages, the largest of which may equal the adult in size.

O. moubata is common on travel routes. Rest-houses are always most infested, and ticks may be carried long distances in mats and bedding. Natives in parts of Africa, and the Boers, try to protect themselves by plastering their huts with mud and cow-dung and by frequently smoking them. Pyrethrum powder

is a valuable preventive. The tick is difficult to dislodge and burning may not completely eradicate it. Old camping sites and native houses are to be avoided, and Europeans must never sleep on the floor. A specific distinction of this species is the series of toothlike lumps on the protarsus of the first pair of legs.

In certain parts of Africa, Abyssinia and Somaliland O. moubata is overlapped by O. savignyi (Audouin, 1827), which prefers market-places and cattle byres in the vicinity of wells. It is distinguished by having eyes, larger processes on its legs and more minutely pitted dorsal surface. It can transmit S. duttoni (in the laboratory) but its exact rôle under natural conditions is doubtful, though suspected in Somaliland. It has been reported from Northern Nigeria, Egypt, the Sudan, East Africa, India and Arabia.

O. lahorensis (Newman, 1908), resembles O. moubata and has an anterior projecting hood. The adult lives in cracks of native houses and walls in Persia and

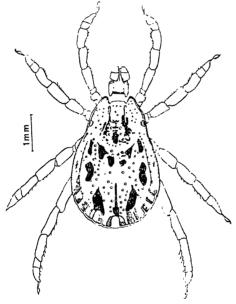


Fig. 329.—Dermacentor andersoni, &. (Nuttall.)

North India. The nymphal stages are passed on sheep. It is suspected of carrying relapsing fever (see p. 188).

O. tholozoni (Birula, 1895), syn. O. papillipes, the "Persian bug," is widely distributed in Palestine, Persia, India and Turkmenistan. In nature it is found in porcupine and jerboa burrows. The male is 4-6 mm. in length, the female 8-9 mm. It transmits Spirochaeta persica (see p. 179) and on biting injects an analgesic substance. Other species in Asia are O. asperus and O. tartakowskyi.

O. talaje (Guerin-Menéville, 1849) resembles O. venezuelensis, and is found from Mexico to Paraguay, also on the Gold Coast. The female measures 5-6 mm. by 3-4 mm. It transmits S. venezuelensis (see p. 179). O. turicata is also a vector from the same region with similar habits.

O. venezuelensis (Brumpt, 1921) is related to the foregoing, and found in Venezuela and Colombia at the higher altitudes, 3,000-5,000 ft. The female is

larger than the male (5-6 mm. by 3-4 mm.). It lives in the walls of native huts in company with bed-bugs, and is very voracious. Eggs are laid in batches of 50-100. Hexapod larvæ, on emerging, feed actively within a few hours on mammalian blood. The nymphs feed without undergoing eedysis, as in 0. talaje, but thereafter they moult after each feed, becoming adult at the fourth. This tick conveys relapsing fever in the districts in which it occurs.

O. hermsi (Wheeler, Herms and Meyer, 1935) is a small ovoid species, sandy-coloured when not engarged. The female (5 mm. by 3·1 mm.) resembles the male (3·8 mm. by 2·4 mm.). It differs from O. talaje in minor details and in the smaller size of the male. It is found in the burrows of many rodents and in

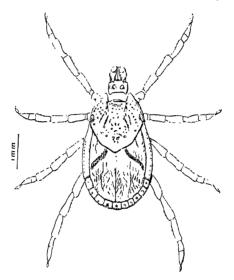


Fig. 330.—Dermacentor andersoni, Q. (Nuttall.)

chipmunk's nest, at an elevation of 4,000–7,000 ft. near Big Bear Lake, San Bernardino County, California. It transmits *S. turicata* in California and Nevada, though tick-transmitted relapsing fever has now been reported from Colorado, California, Texas, Arizona, Nevada, Kansas, New Mexico, Washington and Montana.

- O. turicata (Duges) is closely allied to the foregoing and is found in Mexico, Texas, Arizona, and possibly Kansas. Normally it lives on goats, sheep, foxes and rabbits
- O. erraticus (Lucas, 1849), syn. O. marocanus (Velu, 1919), under natural conditions, lives in burrows far from human habitations. In Morocco it inhabits piggeries. In Senegal and Dakar it transmits Spirochæta duttoni (syn. S. crociduræ), and in Spain and Morocco S. hispanica, in the hexapod larval stage. (See p. 179.)
- O. normandi (Larousse) is found in Tunisia where it transmits Spirochæta normandi, a parasite of gerbils (Meriones shawi).
- Argas persicus (Fisher, 1824) and A. miniatus (Koch, 1844) are common in Northern and Eastern Persia, Syria, Turkestan, Russia, China, Algeria, South Africa, North and South America, West Indies, Western Australia and

Queensland, attacking poultry and man. They live in old houses, in cracks of the walls and floors. Normally they transmit S. gallinarum of fowls and ducks.

IXODIDÆ (HARD TICKS)

There are 12 genera, all parasitic on mammals. They lay eggs in enormous numbers, and the larvæ wait in herbage for their hosts. The chief are Rhipice-phalus and Dermacentor. The former is usually brownish with an angulated basis capituli; the latter is highly ornamented and the basis rounded. Some feed and drop off: others have different hosts (cattle. rabbit, etc.): others, again, have different hosts at different stages. Debility is produced by multiple bites and secondary infections. "Tick paralysis" (see p. 842) is a toxic manifestation from the saliva when the tick has been attached for several days in the region of the head and neck. Coma, respiratory paralysis and death may ensue. In other cases the hypostome, plunged into the skin, may break the capitulum which, being left behind, gives rise to a septic focus.

Rhipicephalus sanguineus (Latreille. 1804) is a brown cosmopolitan species in the tropics, present throughout all months of the year. It is peculiar to the dog, in association with which the whole cycle is completed. Each individual normally has three hosts, one for each of the larval, nymphal and adult stages. The female engorges with blood and then immediately separates from the dog and lays 1,000–3,000 brown eggs which hatch at 25° C.; the larvæ attach thentselves to a new host. At 15–20° C. they can live three to four months. This species transmits the rickettsia of typhus in Texas, South America and South Africa, "fièvre boutonneuse" of Marseilles, and also conveys canine piroplasmosis.

R. appendiculatus closely resembles the foregoing. The larval forms transmit the rickettsia of tick typhus in South Africa.

Hæmaphysalis leachi (Audouin, 1827) does not readily attack man. Its larval and nymphal stages are spent on carnivora, quitting the host at each stage. It is the active carrier of canine piroplasmosis in South Africa and has been incriminated there as a vector of typhus also.

H. humerosa, an Australian species, has been found by Derrick to transmit the rickettsia of Q fever (C. burneti) to man and parasitizes the bandicoot (Isoodon torosus).

Amblyomma americanum (Linn, 1758), known as the "Lone star" tick, from the bright spot on the carapace of the female, is important as the vector of Rocky Mountain and "Bullis" fever in Texas, where it is abundant. Recently the pocket-gopher (a small rodent) which is parasitized by this tick has been found to constitute the reservoir of Rickettsia rickettsii. Found throughout North America and Brazil, it infests dogs, cattle and fowls. The larvæ frequently attack man and live in scrub and high grass (p. 383).

A. hebrœum (Koch), an African species, is widely distributed on lizards and birds, and occasionally attacks man. It has three hosts of the same species. The female may lay as many as 20,000 eggs and transmit the rickettsia of "tickbite" fever in South Africa.

A. cajennense (Koch, 1844) is a large tick found in America from Texas to the Argentine. The males are adorned with a carapace of silvery design. The natural host is the peccary. It transmits the rickettsia of typhus in São Paulo, and, under laboratory conditions, that of Rocky Mountain fever.

Dermacentor andersoni (Stiles, 1908), syn. D. venustus (Banks, 1897), is an important carrier of Rocky Mountain fever in the Western United States, where it is known as the wood-tick. Primarily a rodent infection probably this is normally maintained by Hæmaphysalis, but rodents are also attacked by Dermacentor, so the infection "overflows" to man as in parallel cases of murine

typhus. Tularæmia (p. 284) is also occasionally transmitted. Abundant in the Rocky Mountains the adults appear during the summer, parasitic on horses, big game and other wild animals, and frequently on man (Figs. 329, 330). Larvæ and nymphs occur on small rodents and ground squirrels. The female, when engorged, deposits 5,000-7,000 eggs four to six days after quitting the host. Hexapod larvæ appear on the sixteenth day and in two to eight days engorge. After the larva has fallen to the ground and moulted, the nymph produced can survive for 300 days and, after itself feeding, falls to the ground and moults.

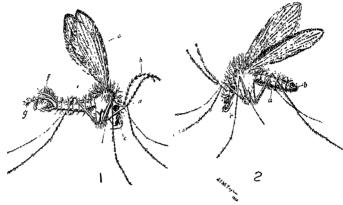


Fig. 331.—Phlebotomus papatasii. × 10. (After Whittingham, "Brit. Med. Journ.")

- 1. Fully developed male image. a, Hairy wings; b, antennæ; c, labial pulps; d, eye; c, latteres; f, classers; g, genital spines.
- 2. Fully developed female imago. Body hairs arranged in tafts; abdomen (a) spindle-shaped; b, ovipositors; c, proboses.

Fully developed males and females can fast two years. After attaching themselves to a mammalian host they copulate in four days. The males remain attached, the females fall to the ground and deposit their eggs. Under natural conditions the cycle takes two years.

D. variabilis (Say, 1821), the dog-tick, is widely distributed in North America, most abundantly on the Atlantic coast. In its immature stages it feeds on small rodents, especially mice; the adults attack dogs and other large animals. It resembles the foregoing. It is the principal vector of spotted fever (typhus) in Central and Eastern United States (see p. 242) and may cause paralysis in dogs. Arsenical dipping of sheep and goats acts as a control, whilst the rodents should be killed off.

Ixodophagus is a small wasp parasite of ticks found in Europe and introduced into America to combat dermacentor.

A vaccine made by grinding up infected ticks (D. variabilis and andersoni) was once employed as a prophylactic against Rocky Mountain spotted fever. It protects for about one year.

INSECTA

PSYCHODIDÆ

GENUS PHLEBOTOMUS (SANDFLIES) (Figs. 331, 332)

Phlebotomi, of which a large number are known, are minute, hairy flies (1.5 to 2.5 mm.) which are readily recognized. The females only suck blood. The

males suck up moisture from any available source. In some people the bites cause local disturbance; in others, none. Sandflies carry sandfly fever (p. 386),

oriental sore, espundia and kala-azar (pp. 162, 173, 143).

P. verrucarum and also P. noguchii (Shannon) transmit Bartonella bacilliformis of Oroya fever (Townsend), and have a wide distribution. P. papatasii, which extends north to Paris and transmits sandfly fever, is widespread through Southern Europe, North and East Africa, Java and India. The body is covered with long hairs, the counterpart of scales. The antennæ have sixteen joints; the proboscis is short and contains the piercing organs. The wings are hairy, pointed and folded roof-wise on the back; venation is distinctly seen on removal of the scales; the legs are long and slender. The abdomen of the female is spindleshaped and provided with small claspers, but the male has two pairs of appendages -the upper and lower claspers-and various other structures known as the intromittent organ, the submedian lamellæ, and the intermediate appendages.

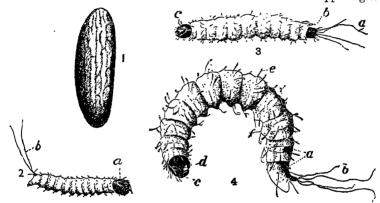


Fig. 332.—Life-history of Phlebotomus papatasii. (After Whittingham, Brit. Med. J.)

Fertilized egg, seven days after oviposition. × 80.
 First stage of larval life, two days old. a, Head with Y-shaped mark and egg-tooth; b, caudal

 Third stage of larval life (dorsal view), thirteen days old. a, Caudal bristles; b, last segment; c, antennæ. \times 20.

4. Fourth stage, twenty-two days old. a, Last segment; b, caudal bristles; c, mandibles; d, labial plate; e, body hairs; f, false legs. \times 20.

Whilst feeding, sandflies are easily disturbed. The stout rostrum is thrust downwards whilst the maxillary palpi diverge and within a minute blood enters the stomach. Sandflies are abundant in the drier portions of the tropics and subtropics, but occur also in wet parts. They fly by night, and shelter in dark corners during the day. The flight is feeble, more like a hop than flight. Their range is usually not more than fifty yards from the breeding places, and they do not rise far above ground level. The maximal vertical distance is 70 feet. Many species do not attack man, but feed normally on the blood of animals such as field mice, even lizards. In the hot deserts of Central Asia sandflies are common in the burrows of gerbils, ground squirrels and tortoises, as well as those of wolves. jackals and foxes. The sandflies are abundant in April and the early part of May but are not seen again till next spring (Petrischeva).

Life-history.— Considerable moisture is necessary to induce oviposition. The eggs (0.385 by 0.12 mm.), laid singly, are black, like those of Aëdes, and reticulated. They are laid amongst rubble in caves or in cracks of masonrv.

The breeding places vary in different parts of the world: in Peru, rubble and loose earth; in Egypt, damp cracks in sand, and in India P. argentipes breeds in broken patches in paved floors, where the soil is contaminated by the fieces of fowls and goats. When organic matter is present, the eggs hatch in six to nine days into twelve-segmented caterpillar-like larvæ with long dorsal bristles on the terminal segment (Fig. 332). Each bears a number of spines arranged in a transverse row, and the larva progresses by slow, undulatory movements. feeding on decaying nitrogenous material, moulds, dejecta of lizards and the bodies of defunct parent flies. The duration of the larval stages varies up to four weeks. There are four distinct stages with a complete moult between each (Whittingham). According to Roubaud, sandflies are heterodynamic, and do not all develop in same manner, so that some individuals remain as larva for considerable periods and hibernation takes place in the larval state. Moisture is necessary; in deserts it is probably obtained from water of condensation. The pupa stage lasts about nine days. It is ochreous-buff and has thoracic appendages free from the body. The integument is covered with minute squames, and there are small spines on the sides of the thorax and abdomen. The image hatches out in the early hours of the morning when atmospheric humidity is high. Adults are crepuscular, nocturnal and active on warm still nights, repelled by sunlight but attracted by artificial light, but some sandflies feed voraciously during the daytime.

The incidence of *P. papatasii* in Mediterranean sandfly fever is definitely related to the number of breeding places. The virus can be transmitted by the bite of the progeny of infected flies, which is probably due to the larvae eating the bodies and faces of adults. In Algeria it is common in autumn; oriental sores occur about six weeks later. In India *P. sergenti* transmits *Leishmania tropica* and *P. argentipes* transmits *L. donouni* (for proof, see p. 147). In kala-azar epidemics in Bengal, 1920–30, the incidence was always greatest in those living on ground floors, thus corresponding to the habits of the sandfly.

In China there is agreement between kala-azar, P. major and P. chinensis and in Italy between this disease and P. perniciosus (96.8 per cent. of which became infected after feeding on infected hamsters).

The following is a brief description of some better known species:-

P. argentipes.—Dark brown, medium-sized, $2\cdot 3-2\cdot 8$ mm. long. On the thorax the dorsum is black, sides light yellow. The wings are broader than in most species. The tarsi are white. Not found outside India it is most prevalent in Bengal and Assam during and after the monsoon.

P. major var. chinensis.—Colour variable, dull greyish to bright yellow. The abdominal hairs are more or less erect dorsally and are of a uniform golden grey. The disc of the wings has a bluish iridescence. The eyes are black and the legs darker than the abdomen, which is clothed with long recumbent hairs and has tufts of longer upright ones on the dorsal surfaces.

P. perniciosus.—The thorax may have dull red-brown spots which are arranged in a triangle. Occasionally a similar spot is present on the vertex of the head. The eyes are black, the thorax and coxe pale, translucent and ochreous. The abdomen is similar and sometimes a pale smoky grey, and the hairs are pallid; the wings iridescent in a strong light with a distinct metallic lustre. The abdomen is densely hairy, the largest arising from the apical margin of the segment, but no distinct tufts as in P. papatasii.

Repellents.—Paraffin is effective, and oil of citronella is widely used. "Flit" and "Parquit" are pleasant and efficient if rubbed into the skin. Dibutylphthalate and DDT are now being employed (see p. 864). Sandfly nots are provided for troops.

The control of sandflies involves removal of rubble, provision of suitable houses and repair of masonry.

For preservation the insects should be placed in a web-like layer of teased cotton-wool, but must not be covered up.

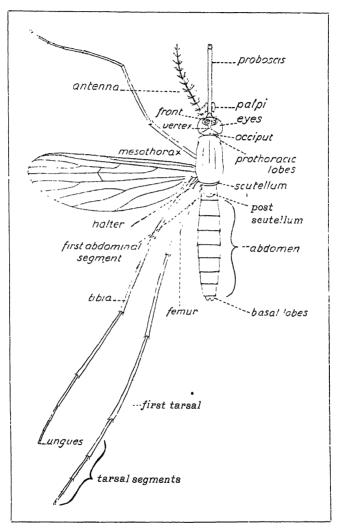
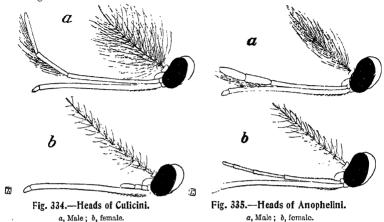


Fig. 333.—Female mosquito, to show anatomy.

CULICIDÆ (MOSQUITOES)

Mosquitoes are not confined to tropical regions; many species (including anopheles) are found even within the Arctic circle. The adult insects feed on vegetable juices; the males almost exclusively. The females of most species

suck the blood of mammals and birds. Many act as carriers of disease (Fig. 333). They lay eggs singly, in groups, or in boat-shaped masses. Hatching out depends upon temperature. In some species the eggs remain dormant throughout the winter, or in drought. In ordinary circumstances the larvæ



hatch out in two or three days, then feed upon organic matter suspended in water. They breathe in air through the respiratory siphon situated near their tails. The larval stage lasts from six days to several weeks, usually ten days. The final is the fourth.

The pupa is free and active for 2-4 days. It rests on the surface and an air-film develops around it. When it is swallowed this film expands and splits

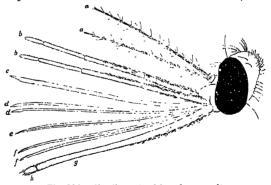


Fig. 336.—Mouth-parts of female mosquito. a, a, Δ antennæ; b, b, palpi; c, labrum-epipharynx; <math>d, d, m and d bles; e, h propharynx; f, f, m axillæ; g, labrum; h, labella.

the pupal case. When more air is swallowed, the mosquito works its way out. The abdomen is contracted, and blood is forced into the wings, which then expand. The mosquito rests $\frac{1}{4}-\frac{1}{2}$ hour on its pupa case until its wings and body have hardened.

In Europe the whole process from egg to imago occupies about one month, but in the tropics seven to ten days. During colder weather development of the larva is temporarily suspended and the surviving adults, especially females, hibernate in dark and sheltered places. In this manner the species is carried over the winter. In some varieties there is evidence that hibernation is carried out in the egg and larval stages. The life of an adult mosquito is variable, but some species, if supplied with suitable food, can live for several months.

Although most mosquitoes are singularly local, yet migrations are occasionally observed, and the insects are often transported great distances in ships, railway carriages or air planes, and widely diffused. One or two species in most genera are domestic in anopheles, culex, theobaldia, etc. There are over a hundred species of Aëdes and of these three only are domestic: others are jungle-dwellers. The majority are nocturnal.

Identification is necessary to recognize the structures by which they are classified. There are three recognizable divisions: head, thorax and abdomen. (Fig. 333). The head is rounded and attached to the thorax by a slender neck.

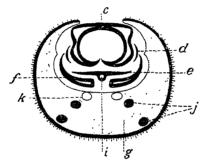


Fig. 337.—Section of mosquito's proboscis.

(Adapted from Nuttall and Shipley.)

c, Labrum-epipharynx; d, mandible; e, hypopharynx; f, maxilke; g, labium; i, salivary duct; j, muscles; k, trachea.

It is provided with large eyes, antennæ and mouth parts. The antennæ (Figs. 334, 335) are composed of fifteen segments. Each bears a whorl of hairs in the female, but in the male the hairs are profuse, giving a bristly appearance. The mouth parts consist of a proboscis in the female fitted for piercing and sucking. Externally, a chitinized labium (Fig. 334) encloses the other mouth parts, except the maxillary palpi, and ends distally in two pointed labellæ clothed with scales and hairs. The labrum is a hollow cylindrical tube with a narrow opening on the ventral surface. In the act of biting, the labellæ part and are applied to the surface of the skin, forming a sheath for the delicate piercing organs, and do not enter the wound made for obtaining blood. Within is the labrum-epipharynx, composed of two thin chitinous lamellæ imposed on each other, forming a V-shaped channel which is open on the ventral surface. This extends along the whole length of the labium and ends in a sharp point. Lying directly beneath the labrum-epipharynx, closing the ventral slit, is the hypopharynx, consisting of a thin, chitinous lamella, fitting closely to the ventral surface of the labrum-epipharynx, thus forming a tube through which blood is sucked. In the longitudinal chitinous thickening runs a very fine channel extending from base to tip of the hypopharynx; through this the salivary secretion is poured into the wound (Fig. 337). The mandibles are delicate chitinous structures at the side of the hypopharynx. The labium buckles in

the act of biting, and the mouth parts emerge. Each of these tapers slightly towards the tip, ending in a sharp point. The maxillæ are more robustly constructed, but have the same general form, the tip is generally provided with a row of backward projecting teeth. The maxillary palpi consist of three to five segments. In the male the mouth parts are greatly modified and not adapted for piercing. The maxillary palpi are elongated, extending beyond the tip of the proboscis, but the mandibles and maxillæ are greatly reduced and may be lacking altogether.

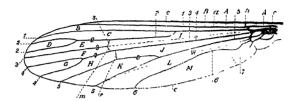


Fig. 338.—Wing of Culex (male), to illustrate terminology.

In the female anopheles the palpi are as long as the proboscis and usually closely applied, but in the male this feature is not nearly so marked. In both male anopheline and culicine mosquitoes the palpi are as long as the proboscis. The palpi of the male culicines are bushy, and the two terminal joints tend to turn upwards; those of the male anopheles are rather club-shaped.

The thorax is wedged-shaped: the sides form the pleura, whilst the apex bears the legs, and spiracles which are prominent black-rimmed apertures. The various sclerites composing the side of the thorax bear still seta or hairs, arranged in definite groups. The scutcllum is separated by a transverse suture from the mesonotum. In all genera, except anopheles, it is trilobate, and each lobe bears a group of stiff seta. In anopheles the scutchlum is arcuate. The region behind

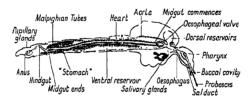


Fig. 339.-Longitudinal section of female mosquito to show anatomy.

the scutellum is known as postnotum and is generally nude. The wings are long and narrow; venation-bearing scales are characteristic (Fig. 336). Situated immediately posterior to the base of the wings is a pair of halteres or balancers, which are sense organs connected with flight.

The legs are long and slender, composed of coxa, trochanter, femur and tibia, and a tarsus of five joints, the last of which is long and slender, especially in

the hind legs. The last tarsal joint bears a pair of claws (pulvilli), which vary greatly in size and shape, but those of the hind legs are generally smaller than those of others. The abdomen is nearly cylindrical, narrow and clongated, consisting of eleven segments. The first eight are quite similar, but the terminal segments are modified for sexual purposes. The terminal segment in the female is pointed. The ninth is reduced, and in the intersegmental area between it and the eighth lies the opening of the reproductive organs. The tenth segment is greatly reduced and bears the basal lobes (cerci) and anal opening. The abdomen of the male is frequently longer than that of the female. The terminal segments are greatly modified and bear clasping organs. In the male the seventh and eighth segments undergo torsion through an arc of 180° after emergence from the pupa, with the result that the eighth tergite and those distal to it become ventrally situated, and the sternite dorsal.

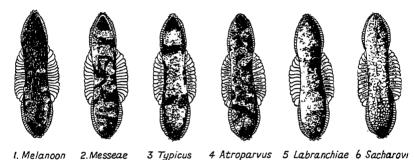


Fig. 340.—Eggs of different species of Anopheles maculi pennis. (After J. F. Marshall.)

The foregut and midgut are ectodermal, lined with chitin, continuous with the cuticle. Columnar epithelium lines the midgut. The entrance of the five Malpighian tubes marks the junction of hind and midguts. There are three salivary glands on each side. Various diverticula branch off from the gut (see Fig. 339).

Dissection of mosquito.—After chloroforming, the insect is placed on a slide in a drop of saline; the wings and legs are cut off. For dissection of the salivary glands one needle is applied behind the head and a second held horizontally on the thorax. The head is pulled forward, dragging out the salivary glands: this movement should be done in stages, with frequent jerks. Next the head is removed from the glands and the preparation covered with a coverslip. Examined under fith lens, refractile sporozoites can be seen in a malaria infected anopheles. For dissection of the gut, the rectum is pressed up and down with pointed needle and then the body is cut through near the termination of the rectum. Gentle traction draws out the rectum and gut in a series of jerks. These are covered with a coverslip and examined. The tracery of fine black lines over the stomach denotes the tracheæ, and this feature can be used for focusing down with fith lens in order to demonstrate malarial occysts.

CLASSIFICATION

There are 1,600 species of mosquitoes in the world, divided into sub-families.

1. Megarhinus, in which the basal half of the proboscis is rigid and the distal half flexible. The adults feed on flowers, whilst the larvæ are predaceous.

- Culex, in which the pulpi of the female are less than half as long as the proboscis, the scutellum is trilobed and eggs are laid in rafts.
- 3. Aèdes, in which the palpi and trilobed scutellum are as in (2), the abdomen of the female is pointed, and the eggs are laid singly.
- 4. Mansonia, in which there are broad asymmetrical wing scales, and the first sets are absent on the upper side of the wing vein. The larvæ have a specialized respiratory syphon.

FAMILY ANOPHELINI: (Genus anopheles)

The palpi in both sexes as long, or nearly as long, as the proboseis. The scutellum is rounded, without lobes, and the eggs are laid singly.



Fig. 341.—Larva of Anopheles maculipennis Meigen, showing breathing position at surface of water. (After Howard, "Bull. United States Dept. Agr.")

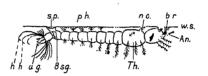


Fig. 342.—Larva of Anopheles maculipennis to show feeding position. (After J. F. Murshall.)

An, antenna; a.g., anal gills; br., month brush; h, h, hooked (graphel) hairs; n. o., notched organ; p.h., palmate (float) hairs; s.p., spiracles; Th., thorax; w.s., water surface; 8 sg., 8th abdominal segment.

Anophelini were divided by Edwards into three genera: Chagasia (scutcllum slightly trilobed), Bironella (scutcllum evenly rounded, wing with stem of median fork wavy) and Anopheles (scutcllum evenly rounded, wing with stem of median fork straight). The genus includes 160 species. The commoner kinds, whilst resting, hold the proboscis, head and abdomen nearly in a straight line, and give the appearance of a splinter lifted at an angle from a surface; exceptionally, as in A. culicifacies, the resting position adopted is more culex-like (Fig. 364). Usually the hum produced by these mosquitoes is low-pitched, almost inaudible unless close to the ear. Most of them are not strong fliers, and seek cover, even in a moderate breeze, yet dispersal flights may carry individuals ten or more miles from their breeding places. The flight range is 2-2-7 miles.

Fertilization of the female takes place directly upon emergence from the pupa. The males emerge first, and swarm over the breeding places awaiting the females; when the insects dart into a dancing mass, mating occurs. Most species require wide spaces for mating, rendering it difficult to propagate them in captivity. Over-wintering females are fertilized by the last brood of the males during autumn; the eggs are deposited soon after the spring dispersal flight. The

boat-shaped eggs (Fig. 340), with rare exception, having an investing membrane inflated laterally to form a pair of floats. They are laid singly on the surface of the water and hatch in two to three days. The larva during growth undergoes four moults. The cuticle is laid down by a single layer of epidermal cells, which form a new and folded cuticle, the larva inflating itself by swallowing water before the new cuticle hardens. The larva feeds on small suspended particles swept into its mouth by two feeding brushes which can be folded under its head. When anopheles larvæ lie on the surface, the dorsal aspect of the thorax and abdomen faces upwards, but the head is rotated 180° so that its ventral surface lies upwards (Fig. 342). Food consists of living organisms, bacteria and protozoa obtained beneath the surface. The head of the larva is complex: the central portion is known as the clypeus, the anterior plaque as the preclypeus. It has a pair of short antennæ, eyes, a pair of feeding brushes, and preclypeal and clypeal hairs. The respiratory opening is composed of two laterally-placed spiracles in the 8th abdominal segment. There is no respiratory syphon. (Fig. 341.)

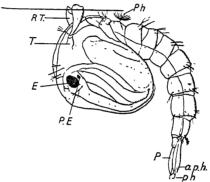


Fig. 343.—Pupa of Anopheles maculipennis. (After Marshall.)

E, eye; P, paddle; P.E., pupal eye; P.h., paddle hair; A.p.h., accessory paddle hair; R.T., respiratory trumpet; T, trachea leading to anterior thoracic spiracle.

The larva maintains itself on the surface in a horizontal position by a row of dorso-abdominal plaques, palmate hairs and a series of scales in rosette form on its back. The terminal segment is provided with four anal papillæ (gills), dorsal and ventral, and swimming brushes (Fig. 344). The gills have no respiratory function, but take up chlorides from the water. The eighth segment is adorned with a chitinous comb. Tracheæ run the length of the body with branches extending to all regions. Small glands secrete a waxy substance near the spiracles, which therefore cannot be wetted. (It is important to note this fact in oiling water to kill larvæ.) Respiration also takes place through the cuticle, but the oxygen intake from the water is not sufficient to maintain life, except when the temperature is low and metabolism is reduced. The pupæ are distinguished by the shape of the respiratory trumpets and by the presence of a paddle hair (Fig. 345).

Only the adult females are able to suck blood, but they do also feed on fruit juices in late summer when the grapes are ripe. The males feed on flower and fruit juices. The females can survive, but cannot lav eggs, on a diet of vegetable juices; this function needs a rich protein meal, and they usually suck blood at night, but times vary with the species, and in dark rooms they may feed during the daytime.

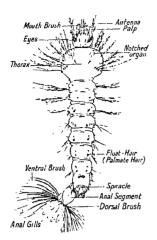


Fig. 344.—Larva of Anopheline (A. maculi pennis) from above. (After Marshall.)
The anal segment is twisted round so as to display the dorsal and ventral brushes.

The capabilities of any particular species of anopheles to transmit malaria are regulated by a number of factors, such as the numbers present, whether the parasites of malaria can complete their development in the mosquito. anthropophilism (readiness to feed in nature on human blood), and whether the insects feed in the jungle or readily enter houses. Some species prefer swamps when breeding, The term "zoophilism" is employed when the insect is deviated by animals, i.e., cattle, as habitually happens with races of A. maculi-The nature of the vegetable food of the female is important, as some substances interfere with development of the malaria parasite. A species proved to be a natural carrier in one situation does not necessarily play an important part somewhere else, e.g., A. aconitus in Java. In North America A. crucians is found to be an efficient carrier when bred in brackish water. subpictus (rossii), as a rule, plays little or no part in the transmission of malaria in India, but yet during an epidemic it may be found infected up to 8.6 per cent, in Java.

There is a striking correlation between the incidence of malaria and of anopheles as seen in the case of A. punctulatus which occurs on some islands in the South Pacific, but not on others. Where this species occurs there is malaria; where it does not, there is none. Nomenclature is a vexed question. A great many species have been renamed in recent years. In case of doubt recourse should be made to the Index Insectorum and the monumental publications of the British Museum by Edwards. For example, Anopheles rossii, one of the first Anopheles to be described and experimented upon by R. Ross, is now found to be the same as A. subpictus.

In making a malaria survey all adult female anophelines in and around the house should be collected and dissected to find out which species is infected. It is necessary to dissect several hundred insects and to examine the gut and salivary glands. An infection rate of 5 per cent, is usually heavy, though higher rates are recorded in Africa. Adults and larvæ should be identified to determine dangerous carriers. The locality should be studied for at least a complete year. Seasonal transmission is important: one species may be responsible in spring and another during the autumn.

Identification of the many diverse species of anopheles is specialized work. The following points are of specific importance: size, general colouration, colour of frontal tuft on the head (yellow or white), and character of the scales. (Fig. 345.) The distal half of the proboscis may be pale, the palpi may be smooth or shaggy, depending on the scales. The markings (banding) on palpi may be entirely dark or there may be pale bands. The general colouration of the thorax and scales on the mesonotum is helpful. The scales on the wings may be entirely dark, or may have four pale areas. The third voin may be entirely dark or pale. Pale spots may be present on the fringe opposite the various veins. Speckling, or banding, of the legs is an important point, and the presence or absence of lateral tufts or buttons of the large scales on the abdomen (Fig. 346). In scientific entomology, larval characters of the last stage, or fourth instar, are

important as a basis of classification. These features are too intricate to be detailed here (see J. Smart, "Insects of Medical Importance"; British Museum Publications).

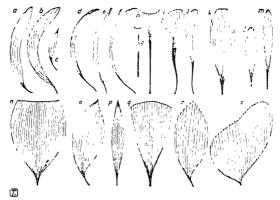


Fig. 345.—Graphic key to distinctions based on scale characters.

a,b,c, Narrow curved scales; d,e,f, hair-like curved scales; g,h, upright forked scales: i,i, long, twisted scales; k, large lanceolate scale; l,m, small narrow lanceolate scales; n, large expanded scale; o,p, spindle-shaped scale; q, broad flat scales; r,s, broad irregular scales.

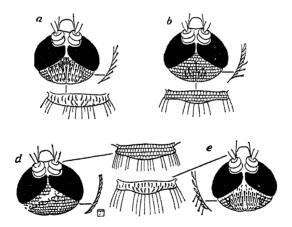


Fig. 346.—Various types of "scale vestiture."

(Such scale characters are now regarded as specific and not of generic importance.)

a, Anopheles, head, scutellum, and lateral view of head scales; b, Ardes (Stegomyia) ægypti, head scutellum, and lateral view of head scales.

d, Megarhinus, head, scutellum, and lateral view of head scales; e, Culex, head, scutellum, and lateral view of head scales.

A. maculipennis (Fig. 347) has a world-wide distribution as the most important carrier of malaria. It is nocturnal in habits and is most active between midnight and 2 a.m. It indulges in a marriage flight and a constant change of resting place appears indispensible to its existence, so that the anopheline population may become entirely changed within a few days.

Hackett and Missiroli showed that A. maculipennis is not a homogeneous species, but a collection of widespread varieties which may possibly represent species. Those generally accepted are:

A. maculipennis, Meigen, or typicus, which lays eggs with two simple bars;



Fig. 347.—Anopheles maculipennis, female. 1

A. m. messew, Falleroni, which lays dark barred eggs; A. m. melanoon, Hackett, which lays uniformly black eggs; A. m. atroparous, Van Thiel, which lays a dark grey and dappled egg; A. m. labranchiæ, Falleroni, which lays a light grey and dappled egg; and A. m. sacharori (or elulus), Edwards, which lays a uniformly grey egg (Fig. 340).

These varieties are identified by the markings of the eggs and character of the floats, by the larval hairs, and by the external harpaginal spine of the adult male. Authorities are of the opinion that the egg-types provide a satisfactory method of dividing A. maculipennis (Fig. 347), but Ungureanu and Shute have demonstrated that the adults can be distinguished from one another by the different shapes of the wing scales. In atroparvus the scales are slender and taper gradually towards the tip; in messace they are wider and taper acutely; in typicus the scales are wider and taper less acutely than in

messee, but more acutely than in atroparous; in sacharori the scales are widest in the centre and taper gradually.

A. maculipennis typicus has not been found in England, but in Norway, the Black Forest and the Hartz Mountains; messee in the fresh waters of Europe, its southerly range being Italy and the Balkans; melanom favours the rice-fields of North Italy and South-East Spain; atroparvus is a salt-water breeder on the North Coasts of Europe; sacharovi (elutus) replaces atroparvus in the south; labranchiæ takes the place of atroparvus in North Italy and is the dominating variety in the Campagna. Atroparvus and messee are the only two varieties found in England.

The subdivisions of A. maculipennis are supported by biological differences in breeding-places, sexual behaviour, and habits. Atroparvus breeds in salt water: messeæ in fresh. Atroparvus does not go into complete hibernation. All varieties are equally susceptible to malarial infection, and although some prefer to feed on animals, there is never any insurmountable barrier. In almost the whole of northern Europe A. maculipennis lives on domestic animals, and man is protected from malaria by the deviation of anopheles by animals. In the malarious regions of southern Europe maculipennis bites man persistently. The principal reason for differences in behaviour in the north and south, is that the anopheles population of the latter region consists of varieties—labranchia and sacharovi—which feed upon man. The races typicus and melanoon are rarely associated with malaria. Messee is deviated by animals and goes completely into hibernation in winter. A. occidentalis, Dyer and Knab, is identical with A. maculipennis, and has the same biological varieties. It occurs along the northern borders of the United States, and in southern Canada, dipping in a southerly direction along the Pacific coast into Mexico, where it is now known as A. maculipennis, var. freeborni.

¹ A magnifying glass is necessary for identification from these drawings.

Sinton and Shute, in a report upon the longevity of mosquitoes in relation to the transmission of malaria in nature, obtained no evidence that, among healthy specimens of A. maculipennis. var. atroparvus infected with Plasmodium vivax and kept under conditions favourable to longevity, there is any noteworthy decrease in life as the result of the plasmodial infection.

Although available evidence adds little support to the suggestion that plasmodial infections may be a serious cause of mortality amongst anopheline mosquitoes in nature, especially A. maculipennis, var. atroparvus, it does not offer any satisfactory explanation of the reason why some anophelines are important as malaria-carriers under natural conditions, while others are not.

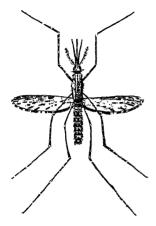


Fig. 348.—Anopheles gambiæ.¹ × 6

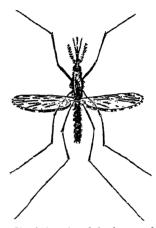


Fig. 349.—Anopheles funestus.¹ × 6

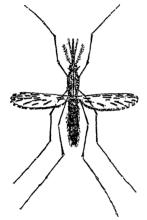
A. gambiæ (A. costalis) (Fig. 348) is the most widespread and dangerous malariacarrier in Africa. Recently it has extended its range northwards into Upper Egypt. In 1930 it was introduced from Senegal into Natal (Brazil), spreading with great rapidity and concurrently with epidemic subtertian malaria, but it has now been exterminated (1942).2 It breeds in almost any collection of water, if fully exposed to the sun, such as wayside puddles, borrow pits, wells, flood-water, pools in river beds, slightly brackish or muddy, as well as clear water. In Somaliland during the dry season it æstivates in deep wells, thus accounting for its apparent absence. Normally it does not breed in rivers except when they are partially dried. It is domestic in habits, and bites man readily. Another allied species, A. melas, described by Thompson and established as a species by Ribbands, is a salt-water breeder (46 per cent. sea-water) and is co-extensive with the Avicennia mangrove. It is a melanistic coastal form extending from the Gambia to Nigeria. There is often an extra band on the palpi of the female. The egg differs in possessing an inner white rim; there is a difference also in the larval pecten. About 4 per cent. are naturally infected with malarial sporozoites.

Avicennia nitida mangrove is associated with a sea-grass and resembles an apple tree in appearance, growing in scattered, isolated "orchards" above neap-tide.

¹ A magnifying glass is necessary for identification from these drawings.

² International Health Division of the Rockefeller Foundation (Soper and Wilson), *Anopheles gambia* in Brazil, 1943. The Rockefeller Foundation.

A. funestus (Fig. 349) is the second most widespread and important malaria mosquito in Africa with the exception of the North. For breeding it needs shade in grassy-edged, sluggish streams with clean water; it never breeds in puddles without vegetation. The adult is domestic, bites man readily, and enters houses. It usually breeds in streams outside towns and is therefore a more rural species, being particularly dangerous in streams of foothills which are independent of local rainfall. The sporozoite rate may be 5 per cent. and endemic malaria is kept going by this species. In North Africa and in Egypt these two species are replaced by A. multicolor and the brownish-coloured A. sergenti, the former of which usually breeds in brackish water, the latter in freshwater puddles. In the Delta region A. pharcensis plays a part in malaria





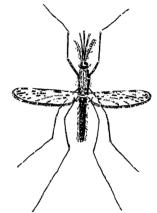


Fig. 351.—Anopheles stephensi.1×6

transmission. In Israel and Syria A. bifurcatus breeds in wells and plays a definite rôle in endemic malaria during the winter season.

There are between 40 and 50 species of anopheles in Asia.

A. superpictus (Fig. 350) is often found in streams and in the shelter of rocks, especially in partially dried-up rivers in summer time. In Israel it hibernates in caves. Control is difficult.

A. stephensi (Fig. 351) is a town mosquito, the chief malaria-carrier in Bombay, but in Calcutta is almost a non-carrier, feeding mostly on cattle. It breeds chiefly in wells, and in closed cisterns, roof gutters and barrels, in close contact with man, who is readily infected. As with A. maculipennis there are subvarieties distinguished by their eggs. There are two main races, urban and rural.

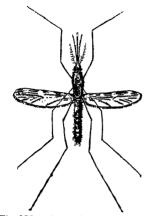
A. subpictus and A. vagus are similar in appearances and habits. They are the commonest species in India and breed in anany situations, in puddles, ponds and rice fields. Both are common in houses. They are mostly zoöphilic and therefore not of importance as malaria carriers. In Java A. subpictus carries malaria and breeds in brackish water.

A. culicifacies (Fig. 352), is the chief vector in India and Ccylon. This species, like Culex, assumes the horizontal stance. In malaria epidemics such as that of 1933-35, 20 per cent. are infected. This Anopheles breeds in sunlight, in clear water pools, especially dried-up rivers (as after drought in Ceylon), small irrigation channels and seepages from larger canals, wells and ornamental

¹ A magnifying glass is necessary for identification from these drawings.

waters. It becomes abundant after excessive rain with high atmospheric temperatures. The transmission season therefore is generally brief, about six weeks. In Eastern India, especially in Bengal, this species is scarce. In some parts of India, though prevalent, it is not an important vector.

A. minimus (Fig. 353), fluviatilis, varuna and aconitus all breed in streams, and in habits and appearance resemble A. funestus. Larvæ are found mostly in natural streams, especially those edged with grass, and in irrigated rice fields. (Rice growing in lowland districts in natural swampland, when the water is muddy, is not dangerous, but the same fields in irrigated areas in the foothills of Assam, Northern India and the Philippines are especially malarious.) Thus, in Assam and Northern Bengal, especially in the tea gardens, A. minimus is almost the chief malaria-carrier, being a man-biter by preference and breeding in clear water in drains and streams. In the cold season, when the rivers are in spate, A. minimus retires to more suitable localities. A. fluviatilis, like the latter,





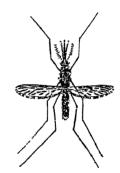


Fig. 353.—Anopheles minimus. 1×6

breeds in the Himalayan foothills down to Southern India, and is responsible for the malaria of the foothills in the tea and coffee estates in Southern India. A. varuna is capricious also in relationship to malaria; it breeds in tanks and reservoirs in Bengal, but is not important in Southern India. It is common in Ceylon, but is not a vector there, but is an important species in Java and Philippines. A. aconitus is not important in India.

All these are absent when the foothills are in a virgin state. Malaria there is really man-made, due to clearing of trees and undergrowth. Control means reversion to shade by planting shade bushes over streams. A. leucosphyrus (balabacensis) is found in India to Celebes, Java to Formosa; its variety hackeri occurs in Malaya. It is an elusive jungle-breeding mosquito and an important vector in Borneo, Sumatra, Celebes, Indo-China and Burma (McArthur, 1951).

A. hyrcanus and A. barbirostris are similar in appearance and habits. They commonly breed together in swamps or cultivated rice fields, but readily take to feeding on cattle, and on this account are usually of no importance in India and China, but in the latter country, as well as in Java, they are important in cattle-free areas.

A. maculatus (Fig. 354) is the chief efficient carrier of malaria in Java and in the rubber-growing districts of Malaya. It does not occur in the natural jungle, unless this is cleared, but is found in streams, seepages, hoof-marks, etc., and

¹ A magnifying glass is necessary for identification from these drawings.

is a man-biter. Shading and covering streams and drains have been effective in prevention. A. maculatus is also common in the foothills of Assam and

Ceylon, but is zoophilic there and consequently not so important.

In dense natural Malayan jungle mosquitoes do not breed, but when it is cleared, A. unbrosus appears and probably carries malaria. This species favours shade; when this is completely abolished it disappears. A. sundaicus (ludlowi) (Fig. 355) breeds freely in Java in salt-water fish ponds, and in cleared mangrove swamps, where the pools are filled with brackish water. Important vectors in Bengal (Iyengar) are: A. philippinensis (in the plains), A. sundaicus (in the delta), and A. minimus (submontane area).

In North America there are only nine species of anopheles, of which three

are regarded as important malaria carriers:

A. maculipennis, var. freeborni, invades houses freely.

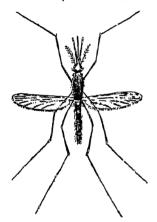


Fig. 354.—Anopheles maculatus.¹ × 6

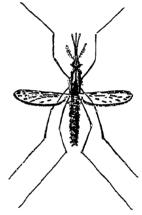


Fig. 355.—Anopheles sundaicus.¹ × 6

A. punctipennis is the most widespread anopheline; it has black and yellow scales on its wings, and breeds in cool shaded pools, seldom entering houses.

A. quadrimaculatus ranges from Mexico to Canada and is the chief vector of malaria in Eastern, Central and Southern United States. The wings have four distinct spots. It breeds in still clean water, and requires sunshine.

A. pseudopunctipennis is widespread from the Argentine through Central America. It breeds in sunlit pools along the courses of receding streams, the larvæ feeding on green algæ. It rarely enters dwellings. This species (like A. maculipennis) can be divided into at least two subvarieties according to the

colour and pattern of the eggs.

A. albimanus (Fig. 356) is the most important anopheline in the Caribhean. Whilst preferring sunlit open pools, it develops also in brackish or salt water. In South America, in addition to the species mentioned, there is another important species: A. tarsimaculatus. A. darlingi has recently been recognized as important carrier in British Guiana, British Honduras, Brazil and Vonezuela. The adults enter houses and bite man greedily. The larvæ are found in collections of water rich in vegetation. A. aquasalis, an important carrier, in coastal regions breeds in salt water. A. bellator is the most important species in Trinidad, where it breeds in the water which collects in epiphytic plants or bromeliads. Its extermination is very difficult.

¹ A magnifying glass is necessary for identification from these drawings.

A. bellator is one of four species of the subgenus Kerteszia. They all breed in water collections amongst the leaves of bromeliads. The principal host plants of these epiphytes are Gravisia aquilegia, Hohengergia stellata, and Witmachia lingulata. Each bromeliad holds from 1 litre of water, thus ensuring the breeding of these mosquitoes throughout the dry season. Some "immortelles" (Erythrina) harbour a hundred or more of these parasites, and they are grown as wind screens to protect the cacao. Under this cover A. bellator is active throughout the day and bites readily at noon. Manual removal of bromeliads is a laborious, but useful, measure, but spray killing by copper sulphate is the method of choice. When treated in this manner bromeliads are slow to regenerate and one application can cover a 10-year period (Gillette).

In Australia, Melanesia, and Polynesia only one species of Anopheles is the vector of malaria, A. punctulatus (Fig. 357) which breeds in stagnant swamps with

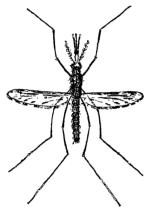


Fig. 356.—Anopheles albimanus.¹ × 6

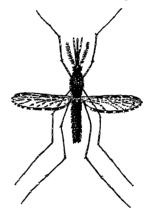


Fig. 357.—Anopheles punctulatus.¹

abundance of algæ, in temporary rain pools, roadside puddles, and even in beached native canoes; it is also found in paddy fields and shady forest pools. It has an unusually wide range of flight, and seeks human blood in preference to that of birds or animals. There are several forms of A. punctulatus, such as A. punctulatus punctulatus and A. p. farauti. All have much in common, though behaviour may differ according to local conditions. Thus A. p. faurati has no preference for either human or animal blood; in A. p. punctulatus anthropophilism is marked. All are more attracted to indigenous peoples than to the white man.

LIST OF ANOPHELES VECTORS OF MALARIA² REGIONS AND TYPICAL BREEDING PLACES

(Those marked with an asterisk are the most important vectors)

EUROPE.

A. algeriensis. W. Medit A. claviger (bifurcatus). S. Europ

W. Mediterranean. S. Europe. Marshes, sluggish streams. Wells, larvæ hibernate in

cisterns.

(Fig. 358)
A. hyrcanus.

Macedonia and E. Medit- Marshes.

A magnifying glass is necessary for identification from these drawings.

²The reader is referred to "Keys of the Anopheline Mosquitoes of the World," 1943, by the American Entomological Society.

A. maculipennis (typicus). (Fig. 347)

*A. maculipennis atroparvus.

*A. maculipennis labranchia.

A. maculipennis messea.

A. plumbeus.

A. sacharovi (clutus).

Rumania, Hungary, E. Czechoslovakia. Yugoslavia, Russia.

(Not in England.) Holland, Germany, Portugal, W. Spain.

Dalmatian coast, Italy, S.E. Spain, Sicily, Sardinia, Corsica.

Same as *typicus*. Russia, N. Europe, England.

S.E. Europe, Russia (Caspian).

Fresh water, including hill regions.

Brackish water, marshes. lagoons.

Brackish water, marshes, lagoons, fresh water in rice fields.

Fresh water.

Tree holes, forest species.

Brackish water, stagnant pools, puddles, sluggish streams.

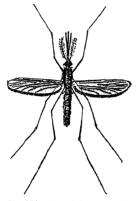


Fig. 358.—Anopheles claviger. \times 6 A. superpictus. (Fig. 350)

E. Mediterranean, Spain, Italy, S. Russia.

Dutch E. Indies, China.

Dutch E. Indies.

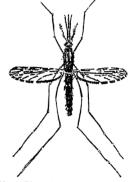


Fig. 359. - Anopheles annularis. (Syn. fuliginosus) × 6

Pools, drains, backwaters, river bods, edges of flowing water.

ASTA. A. aconitus.

A. annularis (fuliginosus). (Fig. 359)

A. balabacensis

(see A. leucosphyrus).

A. barbirostris. (Minor importance)

A. claviger (bifurcatus).

(Fig. 358) A. culicifacies. (Fig. 352)

Borneo Dutch E. Indies.

Urban vector, Syria and Palestine.

S. Arabia, India, Ceylon, Burma, Siam.

India, Ceylon, Turkestan. Java, Celebes.

India, Malaya, China.

Irrigation channels. swamps, ponds, rice fields. Swamps, pools, rice fields.

Swamps, pools, ditches, rice fields.

Wells and cisterns.

Clear, running slow streams. irrigation channels, wells, borrow pits.

Streams and pools. Pools in rice fields. Pools in rice fields.

A. fluviatilis.

*A. hyrcanus.

*A. hyrcanus nigerrimus. (Important vector in some areas)

¹ A magnifying glass is necessary for identification from these drawings.

*A. hyrcanus sinensis. (Important vector in China and S. Japan) (Fig. 361)

A. jeyporiensis.

*A. jeyporiensis candidiensis. (Important vector S.W. China, Tonking)

A. karwari. (Doubtful importance)

A. kochi.

Dutch E. Indies, China, Japan.

S. China, Indo-China, Assam, E. India.

India, Malava, China.

India, Burma, Ceylon.

Dutch E. Indies.

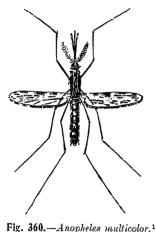
Irrigation channels in rice fields

Rice irrigation channels and streams.

Running water and ditches

Pools in connection with streams and swamps.

Fresh-water ponds, grassy edges of mountain streams.



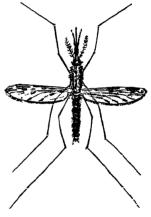


Fig. 361.—Anopheles hyrcanus, var. sinensis.1 × 6

A. leucosphyrus.

Borneo, Labuan, Dutch E. Indies, Java to Formosa.

This mosquito is now regarded as a complex of six members scattered through Asia. The Borneo representative is A. l. balabacensis.

A. maculatus, (Fig. 354)

Philippine Islands, Borneo, Dutch E. Borneo, Duto Indies, Celebes.

A. maculipennis (typicus).

*A. maculipennis atroparvus.

A. maculipennis messeæ.

*A. minimus. (Fig. 353)

A. minimus varuna.

A. multicolor (turkhudi). (Fig. 360)

A. novumbrosus.

Asiatic Russia. Mongolia.

Asiatic Russia.

E. India, Ceylon, Burma, Assam, Indo-China, S. China, Formosa.

India, Ceylon.

Persia, India.

Malaya.

Jungle-breeding mosquitopools, Dirty iungle springs, hoofprints.

Seepage areas in sunlight, or open hill streams.

Fresh water, including hills. Brackish water in coastal areas.

Fresh water, including hills. Grassy springs, streams, ponds, ditches, rice fields.

Pools, ditches, wells.

Pools, irrigation channels and brackish water.

Shade breeder. junglecovered swamps.

¹ A magnifying glass is necessary for identification from these drawings.

1036 ME.	MEDICAL ENTOMOLOGY					
A. letifer (formerly umbrosus).	Malaya.	Coastal hills and plains.				
A. pattoni.	N. China.	Slow mountain streams, rice fields.				
A. philippinensis.	W. India, Bengal, Assam, Burma, Malaya.	Rice fields, lakes, small bodies of water.				
*A. punctulatus.	Borneo.	Stagnant water, pools, puddles.				
*A. stephensi. (Fig. 351)	S. India, Iraq, Ceylon.	Pools and wells, cisterns adapted to towns.				
A. subpictus (rossi).	lndia, Formosa, S. China, Assam.	Polluted pools, often brackish.				
*A. sundaicus (ludlowi). (Fig. 352)	E. India, Burma, Anda- mans, Malaya.	Usually brackish pools.				
*A. superpictus. (Fig. 350)	Asia Minor to India (Pun- jab).	Pools, drains, backwaters.				
A. tessellatus.	Formosa, S. China, Indo- China, Siam, Malaya, Assam.	Pools, puddles, brackish swamps.				
A. multicolor (turkhudi).	Mediterranean, Ethiopia, India.	Rain pools with alge.				
A. umbrosus.	Philippines, Borneo, La- buan, Dutch E. Indies, Colobes.	Peaty marshes in virgin jungle.				
A. vagus. (Minor importance)	India, Andaman Islands, E. Indies, S. China, Formosa.	Small collections of muddy water, ponds and rice fields, also in brackish water.				
Arrica.						
A. algeriensis.	N. Africa (W. Mediter-ranean).	Marshes, sluggish streams.				
*A. funestus. (Fig. 349)	W., S., Central and E. Africa, Congo.	Grassy pools and streams.				
*A. gambiæ. (Fig. 348)	Ibid., also Upper Egypt and Sudan, Arabia, Madagascar, Mauritius.	Ibid. Occasionally brackish water.				
A. hancocki.	Sierra Leone, Liberia, Cameroons, Uganda, Belgian Congo.	Olear water in grassy water- holes, in ditches, wells and swamps.				
$*A.\ hargreavesi.$	W. Africa.	Sides of streams, swamps (vegetation).				
*A. maculipennis labranchiæ.	N. Africa (W. Mediter-ranean).	Brackish pools, marshes, lagoons, rice fields (warmer water than for atropurvus).				
*A. melas. ·	Gambia, Sierra Leone, Nigeria, W. Africa.	Brackish and salt water in mangrove swamps.				
A. moucheti.	C. and E. Belgian Congo, Uganda.	Stream banks, pools (vegetation).				
A. moucheti nigeriensis.	C. Africa, Ethiopia.	Clear water with Pistia and other vegetation.				
A. multicolor. (Fig. 360)	N. Africa deserts, Egypt.	Pools, irrigation channels, brackish and salt water.				
A. nili.	Tropical Africa.	Clear, shaded flowing water.				

	III OI HEELINES	1001	
A. pharænsis.	Egypt, Tropical Africa, Madagascar.	Flooded grasslands, swamps (vegetation).	
*A. sacharovi (elutus).	N. Africa (W. Mediterranean).	Brackish pools, puddles.	
$A.\ sergenti.$	N. Africa, Nile Delta.	Pools, drains, hoofprints.	
*A. superpictus. (Fig. 350)	N. E. Africa.	Pools, drains, backwaters, river beds, edges of flow- ing water.	
AMERICA.			
*A. albimanus. (Fig. 356)	Coastal Mexico, C. America, W. Indies.	Swamps, marshes, streams.	
A. (Nyssorhynchus) albitarsis.	Argentina, Brazıl, Gui- anas, Paraguay, Vene- zuela.	Large ponds, marshes, over- flow areas.	
*A. (Nyssorhynchus) aquasalis (tarsimaculatus, in parte). (Easily de- flected to animals)	Nicaragua, Br. Guiana, Panama, Trinidad, Brazil. Nectar feed- ing by both sexes.	Shaded, or sunlit, brackish, tidal swamps and fresh water rice fields.	
$A.\ argyritars is.$	Brazil, Colombo, Gui- anas, Venezuela.	Pools, ditches, seepage.	
*A. (Kerteszia) bellator and A. (Kerteszia) cruzi	Trinidad, Venezuela, Brazil, "Forest Species," Domestic	Exclusively in collections of water at base of bromeliads, epiphytic on shade trees, such as "immortelle" (<i>Erythrina</i>). Bite man preferably. Enter houses. Active in daytime in deep shade.	
A. crucians.	S. and E. U.S. Coastal, Mexico.	Brackish and fresh water.	
*A. (Nyssorhynchus) darlingi.	Bolivia, Brazil, Colombia, Peru, Venezuela, Ar- gentina. British and Dutch Guiana.	Ground pools, side pools of rivers, with vegetation, muddy road pools.	
A. gambiæ, introduced 1930 into Brazil from Senegal (now exterminated 1942¹)	Brazil (Rio Grande, Ceará).	Grassy pools, streams, brackish water.	
*A. maculipennis freeborni.	Pacific slopes of U.S. and New Mexico.	Clear fresh seepage, over- flow, rice fields.	
A. maculipennis aztecus.	Central Mexico.	Clear and dirty water.	
A. oswaldoi noræstensis.	N. and S. Brazil.	Shaded fresh water in jungle.	
A. punctimaculata.	Central America (Panama, Salvador).	Shaded ground pools with leaves, swamps, sluggish water. Bites man. Houses entered at night. Jungle mosquito.	
$A.\ pseudopunctipennis.$	Argentine (N. W.), Chile, Peru.	Stream beds with algæ.	
$*A.\ quadrimaculatus.$	S. and E. U.S.A., N. E. Mexico.	Pools, ponds, lakes, lagoons, swamps.	

 $^{^1}$ This feat provided the best example of species eradication. Spraying with pyrethrum (Flit) to kill off adults, and Paris Green for larvæ, were the chief methods employed.

All kinds of pools.

N. U.S.A.

A. walkeri.

(Doubtful importance)

Australia and Pacific.				
A. annulipes. (Minor importance)	New Hebrides, Australia.	Pools, marshes, creeks, occasionally brackish water.		
A. bancrofti.	N. Australia, Polynesia.	Shallow, slow - running water with vegetation.		
A. barbirostris. (Minor importance)	N. Australia.	Shaded banks of small lakes.		
*A. punctulatus. (Fig. 357)	Moluccas, New Guinca, New Britain, Solomons, New Hebrides, N. Queensland.	Pools, swamps, puddles.		
*A. punctulatus farauti (moluccensis). (Most im- portant vector)	New Britain and Guinea.	All kinds of water, brackish and salt, clear or standing.		
*A. sundaicus (ludlowi). (Fig. 355)	Moluceas.	Usually brackish pools.		

MALARIA CONTROL

S. AMERICA

British Guiana

Main rector.—.4. durlingi.

Breeding grounds.—Rice fields and sugar plantations behind coastal sea wall.

Intensity.—90 per cent. affected.

DDT campaign in January, 1947. Residual spraying of houses, at intervals of eight months, 1-6 grm. DDT per sp. m. In 1950 interval increased to 1½ years. Results.—None of 2,060 infants born 1949–1950 found positive for malaria. Splear rates.—40–70 in 1945, reduced to 1-5-4 in 1948.

Parasite rates.—From 40-55 per cent. in 1945 to 0-3 in 1948.

Peru

Main vectors.—A. pseudopunctipennis, A. albimanus, A. punctimaculata.

Intensity.—3 million out of 81 million affected.

DDT campaign, 1946, residual spray 2.4 grm. DDT per sq. m. once yearly, houses and stables.

Results.—Malaria incidence 57,993 in 1946 reduced to 30,188 in 1949.

Parasite rates.—6:2-13:4 per cent. before campaign reduced to 0:04-0:3 in 1949.

Venezuela (Gabáldon)

Main vectors.—A. darlingi, A. albimanus, A. pseudopunctipennis.

Intensity. -20 per cent. of 41 million affected.

DDT campaign from 1945. Residual spraying of houses, stables, latrines with 1 grm. DDT per sq. m. every 4 months; then twice dosage every 6 months.

Results.—Reduction in A. darlingi, A. albimanus less so.

Spleen rates.—From 72-7-98-6 per cent. (1941-1945) reduced to 15-5 in 1949.

Argentina

Main vectors.—A. pseudopunctipennis, A. albitarsis, probably A. darlingi.

Intensity.—11 million affected.

DDT campaign, 1947. 2 grm. per sq. m. Residual spraying of houses up to 3½ m. from floor and ceilings at intervals of 3 months during transmission season.

Results.—2,785 cases notified in 1949, compared with 300,000 in former years.

Bolivie

Main vectors.—A. pseudopunctipennis, A. darlingi.

Intensity .- 2 million affected.

 $\overline{
m DDT}$ campaign, 1946. 2 grm. per sq. m. at intervals of 2 months. Results.—Great reduction in spleen and parasite rates.

Brazil

Main vectors.—A. darlingi, A. tarsimaculatus, A. albitarsis and some bromeliad breeding by Kerteszia (A.) cruzi and Kerteszia bellator.

Intensity.—12 million affected.

DĎT campaign, 1947. Residual spraying 1·5–2·5 grm. per sq. m. Limited use also of B.H.C. and Chordane.

Results.—Reduction from 18,927 in 1945 to 3,801 in 1948 and 976 in 1949.

Parasite rates.—From 29.09 in 1948 to zero in 1949.

Ecuador

Main vectors.—A. albimanus, A. pseudopunctipennis.

Intensity.— $3\frac{1}{2}$ million affected.

DDT campaign from 1949. Residual spraying of houses, 2 grm. per sq. m. thrice yearly.

Results.—About 1 million protected from malaria.

N. AMERICA

Main vectors.—A. quadrimaculatus, A. freeborni, A. crucians, A. punctipennis, A. walkeri, A. albimanus.

Intensity.—There has been a general decline in malaria incidence for many years. In 1938 it was estimated that 27 million out of 150 million were seriously affected by malaria, with some 4,000 deaths annually.

DDT campaign. Residual spraying 1 grm. per sq. m. twice yearly in 13 malarious states; increased to 2.1 grm. per sq. m. at yearly intervals. Houses,

walls, ceilings and undersides of furniture treated.

Results.—Malaria mortality per 100,000 in 13 states about 10-12 in 1930 reduced to 0-4 in 1948. Total number of cases in 1935, 135,781 reduced to 4,229 in 1949. Deaths from malaria, 4,252 in 1935 to 142 in 1948.

ASIA

C'eulon

Main vector.—A. culicifacies.

Intensity.—Great majority affected. Malaria zone covers two-thirds of island.
DDT campaign, 1946. Residual spray 2·1 grm. per sq. m. then 1 grm.; more

recently 0.5 grm. at intervals of seven weeks.

Results.—Direct protection for $2\frac{1}{2}$ million and indirect for $4\frac{1}{2}$ million accomplished.

A. culicifacies now rare in houses and larval density is low.

Data for general mortality per 1,000, 24.8 (1928); 20.3 (1946); 14.3 (1947);

and 12.6 (1949).

Spleen rates.—In children 4.5 per cent. (1938); 3.7 (1941); 0.6 (1948); 0.2 (1949), after control had been instituted.

INDIA

Main vectors.—A. fluviatilis, A. culicifacies, A. minimus, A. stephensi, etc.

Intensity.—30 million exposed to malaria.

Bombay State.—Campaign against anthropophilic vector, A. fluviatilis, transmitting from December to June in Kanara district. A second scheme against A. culicifacies, partly zoöphilic, in Dharwar district, transmission season July to November. Residual DDT spraying 0.5-0.7 grm. per sq. m. three 2 me are provided. In the

season. In A. flurialilis terrain only house walls up to 3 m. are sprayed. In the case of zoophilic, A. culcifacies, animal shelters as well as houses treated.

Results.—In Kanara 1 per cent. parasite rate in infants in treated villages, but 13-27 per cent. in untreated. Malaria morbidity reduced by 300,000 per year.

Delhi Province

Vector.—A. culicifacies.

Intensity.—300,000 affected.

DDT campaign since 1947. DDT at 0.54 grm. per sq. m. applied twice yearly

to houses and stables.

*Results.—Spleen rates in rural areas fell from 29·3-10·3 per cent. Number of cases in urban districts were 32,405 (1945), 27,868 (1946) and 9,202 (1949). In rural areas the figures were 18,344 (1945), 13,502 (1946) and 4,663 (1949).

EUROPE

Greece

Main rectors .- A. sacharori and A. superpictus.

Intensity.—5 million out of 8 million affected. Second cause of death in infant mortality.

DDT campaigns commenced in 1946 and extended to all malarious regions in 1949.

In urban and semi-urban areas anti-larval work at 0.02 grm. DDT per sq. m, of water surface at intervals of 10-15 days. Large areas sprayed from aircraft at 0.012 grm. DDT per sq. m, at intervals of 23-50 days.

Results.—Spleen rate in children varied from 25-100 per cent. Percentage parasite rate in children from 16-36 before the campaign, fell to 0-1 in 1948. Infant parasite rate became zero. There has been a fall from 100,000 cases of malaria in 1946 with 500 deaths to between 15,000 and 20,000 cases annually in 1947-1949 with almost no deaths.

Italy

Main vectors.—A. sacharovi, A. superpictus and A. maculipennis labranchiw.

Intensity.—Incidence formerly 5,000 cases per million with 200 deaths annually.

DDT campaign commenced in 1946. Spraying once yearly at 1.5-2 grm. DDT per sq. m.

Results.—In 1948 2.012 cases of malaria with 0.08 deaths per million and in 1949, 422 cases per million with no deaths.

Sardinia

Vector .- A. maculipennis labranchia.

Intensity.—23,896 sq. kilometres and population of 1,200,000. Parasite index high.
P. vivax 67 per cent., P. falciparum 26 per cent., P. malariæ 7 per cent.

DDT campaign commenced in 1946. Residual spray 2-0 grm. per sq. m. for adult insects. 1947 Larvicidal campaign with DDT in oil enlarged to embrace whole island 2-5 per cent. DDT + 0-5 per cent. Triton in fuel oil. Final check on eradication 1950.

Malaria has already disappeared; not a single case of primary malaria found in 1949. Some sectors still contain A. maculipennis labranchiæ larvæ.

Cyprus (Aziz.)

Vectors.—A. bifurcatus, A. superpictus, A. clutus, A. algeriensis and A. multicolor.

Intensity.—Almost whole population affected. Area involved 3,584 sq. miles. Island divided into 556 blocks. Specially trained scouts applied anti-larval DDT methods + residual spray to houses commencing in 1946. 19½ tons of DDT used in 1948.

Anopheles eradication campaign terminated at end of 1949.

Results.—Number of cases reported in 1944, 7,686; 1945, 5,908; 1946, 4,489; 1947, 1989; 1948, 406.

Parasite rate in schoolchildren (1947) was 4.5 per cent.; in 1948 was 1.3 per cent. In 1949 no fresh cases of malaria reported. Blood from 275 infants was negative.

Scouts found larvæ only in 34 out of 5½ million breeding places inspected and adult mosquitoes in 6 out of 1 million former adult resting places. No A. elutus larvæ or adults found.

Africa

In Africa as a whole A. gambæ is undoubtedly the most widespread and vicious vector of malaria. Doubts have been expressed regarding the efficacy of DDT against adults of A. gambæ and risks involved in interference with immune state of peoples in endemic areas have been responsible for the less advanced state of malaria control as compared with other countries.

Transvaal

Vectors.—A. gambiæ and A. funestus.

Intensity.—Malaria affects over 1 million inhabitants.

DDT campaign commenced in 1944. Applied thrice yearly to huts and houses at 1 grm. per sq. m.

Results.—Blackwater fever ceased to occur. Spleen and parasite rates fell spectacularly.

Madagascar

Vector.—A. gambiæ.

No results yet available. Extensive campaign of DDT commenced in 1949. Octochlor and B.H.C. also employed. Swamps have been treated for larvæ by helicopter spraying.

Mauritius (Dowling)

Vectors.—A. gambiæ and A. funestus.

Intensity.—Malaria extensive on whole island, nearly every inhabitant affected.

A central zone of the island had already been cleared of malarial vectors; major island-wide programme commenced in January, 1949. DDT sprayed at 2.5 grm. per sq. m. in area extending from central zone to coast twice yearly.

Results.—By June, 1949, A. funestus had disappeared, though A. gambiæ still abundant.

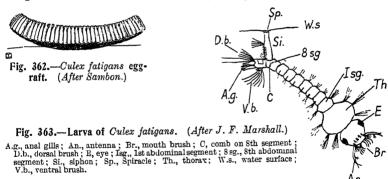
Generally, infant and malaria mortality rates were respectively $27 \cdot 2$ per 1,000 and 150 per 1,000 and 32 per 1,000 before campaign; fell to 16 per 1,000, 91 per 1,000 and $12 \cdot 9$ per 1,000 afterwards.

Percentage spleen and parasite rates were respectively 34.8 and 9.5 in 1948 and

2.8 and 0.36 by 1950.

TRIBE CULICINI

This large tribe contains over 500 species and some 20 genera. The scutellum is trilobed, each lobe bearing bristles. The abdomen is blunt and completely clothed with broad flat scales. The eighth segment of the larva is drawn out into a respiratory siphon with a well-developed pecten and four gills provided with tufts of hairs situated on a projection anterior to the respiratory siphon. Culicines living in water with little chloride have large anal gills. There are no rosettes or



palmate hairs as in anopheles. The pupe are similar to those of anopheles, but the respiratory trumpets are longer.

The following are the main characteristics of culicines in contradistinction to those of anophelines:

(1) The eggs are not provided with air floats, either laid separately or stacked in rafts (Fig. 362).

(2) The larva breathes through a pair of spiracles, situated at the tip of a tail-like tube or siphon, projecting dorsally from the 8th abdominal segment. It hangs head downwards from the water-surface, supported by the capillary action of five hinged valves surrounding the tip of the siphon. It sweeps for floating particles of food with mouth-brushes below surface level, or else dives to the bottom (Fig. 363).

(3) The pupa has cyclindrical respiratory trumpets and usually a branched hair at each "apical" corner of 3-7 abdominal segments. It has no accessory

hair on the ventral surface of the paddle.

(4) The adult has an abdomen densely covered with scales. The female has short and splender palps, from one-tifth to one-half as long as the proboscis. The male has, as a rule, long hairy palps which have a "plume-like" appearance. This mosquito usually rests with proboscis and abdomen forming an obtuse angle, the abdomen being more or less parallel with the supporting surface (Fig. 364).

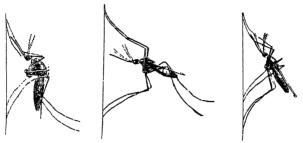


Fig. 364.—Resting position of Culex fatigans, Anopheles hyreanus, and Anopheles maculipenuis.

Culex fatigans (Wiedemann, 1828) (Fig. 365) is a nocturnal species, found in the tropics and subtropics, common in houses; it breeds in water tubs or any collection of water and can be distinguished from anopheles by the position assumed on resting (Fig. 364). The palpi are shorter than the proboscis in the female. This species was first established by Manson (1878) as the intermediary of Wuchereria bancrofti. It also transmits Dirofilaria immitis of the dog and various plasmodia of birds.

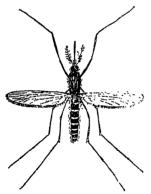


Fig. 365.— $Culex fatigans. \times 4$

C. pipiens (Linn) is the common house mosquito of East and North America and the Pacific coast, ranging through Europe, China and portions of South America. It is brownish-grey and the basal white bands on the abdomen form lateral basal triangular patches. It lays eggs, by preference, in polluted water. It bites viciously and the hum produced is high pitched. It transmits W. bancrofti in Egypt, China, S. America, Queensland and Melanesia, also the virus of human and equine encephalomyelitis. Differs mainly from C. fatigans by character of the male genitalia. According to Marshall there are two species, one, the man-biter, is molestus;

the term pipiens being retained for zoöphilic form, which feeds mostly on birds.

Genus Mansonia (Tæniorhynchus) (Edwards) subgenus mansonioides (Fig. 366)

This genus occurs in tropical and Central America, tropical Africa, and in Asia, especially Malaya, but is less important in temperate North America, Europe, and Australia. These mosquitoes are recognizable by the very broad

asymmetrical wing scales, which are of two colours, white and grey, like salt and pepper, but which do not make conspicuous pale and dark areas. The palpi of the male are longer than the proboscis; the penultimate segment is turned upwards, while the last segment is minute, and is turned downwards.

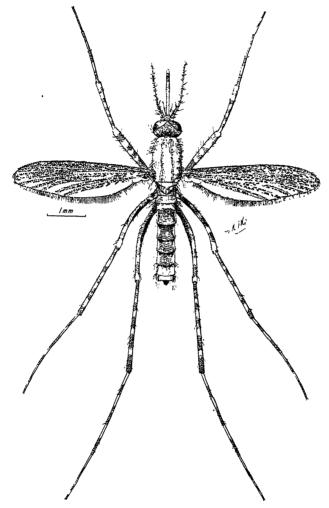


Fig. 366.—Mansonioides annulifera (Theo.) 9 (McKay.)

The end of the abdomen of the female curves upwards, so that only six and a half segments are visible dorsally. The eighth segment is entirely retracted, is of a peculiar form, and carries a row of strongly chitinized teeth on the tergite. The arrangement of these teeth and the shape of the lobes of the sternite are of value in identification. There are five species of importance which are concerned

with the transmission of Wuchereria malayi: M. annulatus, Leic., M. annulifera (Theo), M. indiana, Edwards, M. longipalpis, v. d. Wulp, and M. uniformis (Theo). The larvæ of mansonioides are readily recognizable by the peculiar form of the respiratory siphon, which is adapted for piercing plant tissues (Fig. 367)

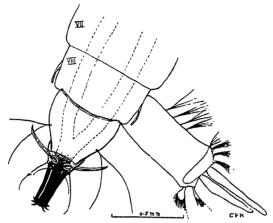


Fig. 367.—Respiratory syphon and terminal segments of larva (dorsal view) of Mansonioides.

(From Bulletins from Inst. for Medical Research, Federated Mulay States; Endemic Filariasis in the F.M.S. (Poyuton and Hodgkin).)

This structure is short, and has a conical base and a distinctive black tip made up of several parts, one of which has a saw edge and ends in a ring of retractable hooks. The known larva closely resemble one another. The pupa are also distinguishable by the form of the respiratory horns which, like the siphon of the larva, are modified for pieroing plant tissues (Fig. 368). Each horn is long and terminates in a narrow, strongly chitinized portion, which bears a pair of

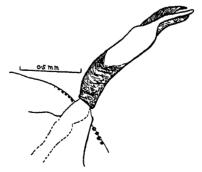


Fig. 368.—Respiratory horn of pupa of Mansonioides.

feather-like structures and ends in a sharp point. All species of mansonia are man-hunters and fierce biters, and attack either in or out of doors. Primarily night-biters, in the jungle they feed at any time. The eggs are laid in small batches, containing a hundred or more, on the underside of leaves of water

plants just above the surface of the water. The most characteristic peculiarity, and the one which defines the distribution of the genus, is the habit of the pupæ and larvæ of obtaining air from the submerged portions of water plants.

The larva of mansonioides inserts its respiratory siphon into the air-containing tissues, and remains there until forcibly removed. The pupæ do likewise. The roots appear to be the part of the plant most favoured. Different species have a preference for certain water plants, and the type of water in which they prefer to grow. M. annulifera, M. indiana, and M. uniformis are most easily found among the roots of water plants floating and growing in exposed situations, especially Pistia stratiotes, a plant which floats with hanging roots in still water. M. uniformis has a preference for the water hyacinth (Eichornia crassipes) and swamp grass (Isachne australis). The food of the larvæ consists of fine particles of organic matter which are freed from coconut husks in the process of coil and rope-making.

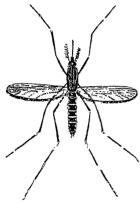


Fig. 369.—Aëdes ægypti.¹ female. × 4.



Fig. 370.—Aëdes scutellaris pseudoscutellaris. Side view, showing buckling of proboscis sheath in the act of biting. × 4.

GENUS AËDES (Meigen, 1818)

Formerly known as Stegomyia, this genus is widely distributed. They are mostly black and white insects with white, silvery yellow bands or spots on the thorax and legs, for which reason they are generally known as "tiger mosquitoes." Certain species ($A. \alpha gypti$ and A. albopictus) are frequently found in ships.

Aëdes ægypti (Fig. 369). Syn.—A. argenteus, Stegomyia fasciata

This occurs all over the tropics and subtropics, 40° North and South of Equator, and in Europe at the level of Gibraltar. It is a domestic species rarely breeding more than 100 yards from houses, and can be recognized by the peculiar lyreshaped design—two dull-yellow parallel lines in the middle and a curved silvery line on each side of the thorax. The proboscis is not banded, but the abdomen is banded basally. The last hind tarsal joint is all white and some of the other tarsal joints are marked basally by light bands. It bites avidly, mostly by night. The eggs are laid in small dark receptacles, e.g., water in tree-rot holes, tins, pots, coconut shells, cut bamboo, sagging eaves, plants, tops of pineapples, sisal leaves, vases in cemeteries, bilges of ships, old beer bottles, and car tyres. When deposited they are white, but darken in a few hours. If kept moist, the larvæ develop in 12–24 hours; they can resist drying for as long as six months. The larvæ then emerge when they are moistened.

 $^{^{1}}$ A magnifying glass is necessary for identification from these drawings.

A. ægypti transmits the virus of yellow fever and dengue (p. 377). Although so widely distributed it does not occur abundantly in Australia, Malay States, China, Africa, and West Indies, where it is replaced by allied species. Under experimental conditions other species may transmit yellow fever, such as A. villatus (sugens), A. apicannulatus, A. africanus, A. simpsoni and Erelmopodites chrysogaster. Abundant throughout S. America and the S. United States, it does not occur in California. A. leucocclaenus transmits jungle yellow fever in S. America.

In the control of aëdes constant attention must be paid to minute details. Legal enactments should be passed for inspection of houses, compounds and buildings. Gutters should be prohibited, and tree-rot holes filled with sand and tar. In most tropical countries old tins are rolled out by rollers operated by the sanitary authorities.

A. vitatus (sugens), with six white spots on the thorax, usually breeds in rock-pools throughout tropical Africa. In Freetown, Sierra Leone, it is usually wild, but readily becomes domestic, and it may act as a vector of yellow fever in West Africa.

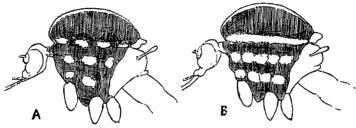


Fig. 371.—Diagrammatic representations of marking on thorax of (A) Ailes albopicius and (B) Ailes scutellaris pseudoscutellaris—lateral views.

A. albopictus (Skuse, 1895) (Fig. 371A) is a commonly distributed species in the East, where it breeds in bamboos near dwellings. In general its habits resemble those of A. agypti, but it is distinguished by the single broad median stripe in the seutum. It is a transmitter of dengue in Japan (see p. 377).

Members of the A. scatellaris complex are found throughout Indonesia and the Pacific. Aždes scatellaris pseudoscatellaris is found solely in Fiji (formerly known as Stegomyja pseudoscatellaris or A. variegatus). A new species, A. s. polynesiensis, has been separated by Marks (1951). It is found in Fiji as well as in Samoa, Ellice, Cook, Society, Austral, Tuamotu and Marquesas Islands.

A. s. polynesiensis closely resembles pseudoscutelluris. There are some small differences in the scales on the scutum, but the main distinction lies in the genitalia of the male. In polynesiensis the basal lobe of the coxite is simple with seta extending nearly to base dorsally, but without stout specialized seta. There are also some minor distinctions in the papillar of the tail of the larvae.

Polynesicnsis is therefore the chief vector of the non-periodic Pacific filaria, Wuchereria pacifica. Members of this group have also been proved to be the vectors of dengue in the Pacific. These two species (pseudoscutellaris and polynesicnsis) are diurnal in habit, bite man, but may also feed on birds. The distinguishing marks are three parallel white stripes on the mesothorax, and the incomplete white abdominal cross bands (Fig. 371 (B)). The larvae resemble those of A. ægypti, but are distinguished by the lateral barbs of the comb scales, which are distinctly smaller and more delicate. The breeding places are peculiar; though readily entering houses, they are not domestic mosquitoes. They breed

mostly in small collections of water containing decaying vegetable matter, in the shells of coconuts, in crevices and holes in trees, in the artificial reservoirs in coconut trees used by Polynesians, in holes in coca-pods gnawed out by Pacific rats; in bottles and tins lying about in the bush. The eggs, larvæ and pupa can withstand considerable desiccation.

Eighteen subspecies are now recognized such as A. scutellaris tongæ, marshallensis, etc., by Marks.

In campaigns against these mosquitoes, the introduction of predatory megarrhine larvæ has been attended in the Pacific by a considerable degree of success. Unless rotten wood is completely excavated, filling in tree holes by a mixture of sand and tar is unsatisfactory. A third species of the scutellaris group is found in Fiji, A. s. horrescens, the larvæ of which are clothed in hairs.

These species are extremely intolerant of sun and wind. Their main haunt is still, shady bush around native villages. Much has been done in the Gilbert and Ellice Islands by the removal of undergrowth, creating a through draught to the trade winds, which render their haunts untenable. Similar measures are being undertaken on a large scale in Fiji by native trained teams.

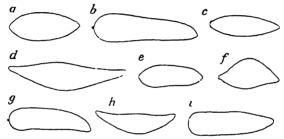


Fig. 372.—Various forms of mosquito eggs.

u, Grabhamia dorsulis: b, Culez pipiens: c, Culez scapularis: d, Mansona titilluns: e, Ardes ægypta: f, Tæniorhynchus fulvus: g, Culex fatigans: h, Janthinosoma lutza: 1, Tæniorhynchus fasciolatus.

Sabethini (Sabethoides)

These are jungle mosquitoes, suspected of transmitting jungle yellow fever in Brazil. In all three stages of their existence they are so characteristic that they have been distinguished as a separate tribe. The adults have a metallic lustre. The scales of all parts of the body are flat. There is a pair of very large procumbent bristles projecting from the crown of the head. The antennæ are similar in both sexes; the palpi short in the female and usually also in the male. The larvæ are generally predaceous and live in the water which collects in the axils and bracts of leaves, or is secreted by pitchers or other modified parts of plants. They are usually rather hairy and have smooth or stumpy antennæ. A siphon is present and there is a single row of scales on the sides of the eighth abdominal segment. The pupæ are characterized by the conspicuous fan of bristles at the postero-lateral angles of the eighth and ninth abdominal segments and by the small tail-fins. The most widespread species is *Trichoprosopon frontosus* which is widespread in S. America and transmits yellow fever by its bite under laboratory conditions.

FAMILY CERATOPOGONIDÆ (midges, gnats)

These are very small (1-3 mm. in length), slender, bloodsucking gnats, generally known as midges. In biting habits they resemble Simuliidæ and are frequently mistaken for them. The antennæ are plumose in the male, pilose in the female.

Amongst twenty or more genera comprising the family, the most important from the medical aspect are *Culicoides* (Fig. 373), *Ceratopogon* and *Leptoconops*. All bite man viciously, mostly at dusk or night.

Genus Culicoides.—(1·4-1·8 mm. in length). The eyes are large. The antennæ are long and thread-like; the wings contain pigment in the membrane, not scales like mosquitoes. The eggs are white, small and oval, and laid on algæ in shallow water. On hatching, the larvæ wriggle in the mud. They are usually red and known as "blood-worms." They have four pairs of gills. The pupa is furnished with no exterior easing, so that the wings and legs are fused to the thorax. Two long respiratory trumpets are present. The adult





Fig. 373.—Culicoides graham: $\varphi \times 50$. (After Byam and Archibald.)

Fig. 374. -Simulium damnosum. \times 10.

emerges after three days. Culicoides austeni and C. grahami have been proved intermediary hosts of Dipetalonema streptocerca. They are night biters and prefer dark skins. C. furens transmits Mansonella ozzardi in Guiana and C. parænsis does so in Antigua.

FAMILY CHIRONOMIDAE

These are midges which look like mosquitoes, but do not bite man. When resting they raise the front pair of legs. The proboscis is vestigial, and there are no scales on the wings. They occur near lakes and rivers in large swarms.

FAMILY SIMULIDA

The simulidæ include "buffalo gnats," black flies and "turkey gnats." Generally small (1 to 5 mm. long), they are blood-sucking, with blade-like piercing female mouth parts, which in the male are more or less rudimentary. Characteristic is the prominent hump caused by strong development of the scutum and reduction in size of the presentum. The antennæ are composed of ten to eleven joints. In the female the eyes are distinctly separated, but closely set and prominent in the male. The palpi are composed of four joints. The wings are broad and irridescent, with distinct alular, and the venation is characterized by prominence of the costal veins.

They occur in enormous numbers in favourable localities during late spring and early summer in northern countries, and are particularly abundant in the

north temperate and subarctic zones and also in the tropics.

They breed by preference in running water and shallow mountain streams; sometimes in roadside ditches. Both sexes feed on mammalian blood and are extremely voracious, attacking cattle and man. The bites are most painful. In cattle they may cause severe loss of blood and consequent anaphylactic phenomena. Death may result from cedema of the lungs.

The eggs, in masses of 300-500, are laid in water, and are triangular and yellow, becoming black at a later stage. The larvæ emerge in two or three weeks and immediately attach themselves to stones. They are cylindrical, with posterior swellen extremities. In colour they are brown to black—consist of twelve segments. The posterior end is provided with toothed disc-like suckers composed of two modified parapodia. The pupa attaches itself to aquatic weeds;

it is encased in a cocoon open at the top from which a pair of branching gills emerge. Oxygen is obtained by diffusion through the cuticle. Pupal period is 5–6 days. Pupæ are provided with respiratory filaments attached anteriorly to the dorsal portion of the thorax.

The various species of simuliids in West and Central Africa live under ecological conditions similar to those found in Guatemala. It has been noted that the African species bite low on the body, and there seems to be a relation between the position of the bites and the situation of the adults of Onchocerca volvulus

which they transmit.

The following species are common in various parts of the world. Simulium damnosum, the "jinja" fly of Central Africa (Fig. 374); S. reptans, Europe; S. indicum, "potu" or "pipsa" fly of India; S. vittatum in North and South America; Eusimulium avidum, E. ochraceum and E. mooseri, vectors of O. volvulus in Guatemala (p. 776), and the last two in states of Oaxaca and Chiapas, Mexico, where they are known as "mosquito negrito" or "alazan." S. damnosum and S. neavei are intermediaries of Onchocerca volvulus in Central Africa. The larvæ and pupæ of the latter species are found in Kenya (in cascades of Kipsonoi river) attached to crabs—Potamon (Parathelphusa) niloticus. This is known as a "phoretic association" as in other species in association with pupæ and nymphs of the mayfly.

MUSCIDÆ (FLIES) BLOOD-SUCKING FLIES

Horseflies, gadflies and deer flies are large insects with well-developed bodies (10-25 mm.) They are strong fliers, notorious pests of cattle and deer, and readily attack man, especially *Chrysops*. The males feed on vegetable juices, and do not bite warm-blooded animals. The eyes are very large and widely

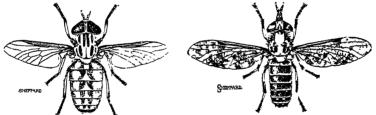


Fig. 375.—Tabanus ustus, & Nat. size. Fig. 376.—Hæmatopota, \mathcal{L}_{2} . (Partly after Austen; by permission of Trustees of Brit. Mus.)

separated in the female, contiguous in the male. The antennæ consist of three dissimilar segments; the third is usually elongated. The venation of the wings is complex; the second longitudinal vein is not forked. The family Tabanidæ includes gadflies, Tabanus (Fig. 375), Hæmatopota (Fig. 376), Pangonia (Fig. 377), and Chrysops (Fig. 378). They are most frequent near water, being semi-aquatic in their breeding habits, some breeding in moist earth, or leaf mould. Eggs are laid near water in layers, and are narrow and cylindrical (1·0-2·5 nm.), vary from 100-700 and are covered with a secretion binding them tightly together. The larvæ are slender and cylindrical, have 11 segments, a head, and taper at both ends. The pupæ resemble those of lepidoptera. Adult flies emerge from the pupa case through a slit along the dorsum of the thorax. The male Chrysops does not feed on blood.

Genus Chrysops is found all over the world, but subgenus, Kleineana, which contains all the known and suspected vectors of L. loa, is limited to Africa. C.

silacea and C. dimidiata are restricted to rain forests.

The breeding places of *C. dimidiata* and *C. silucea* have only recently been discovered in muddy pools along the Kumba River in the Cameroons by Chwatt and Jones.

Chrysops discalis is groy or yellowish-grey; in the female black spots are seen on the abdomen. The male (8-10 mm.) is predominantly black, with yellowish-grey spots on the abdomen. This fly is a transmitter of tulerremia in Central and North America, where it is a common species.

- C. dimidiata (v.d. Wulp) (Fig. 378), a West African species, is particularly abundant during certain times of the year in Nigeria and the Cameroons, and acts as an intermediary of Loa loa (p. 996). In the Cameroons 7·2 per cent. of wild-caught flies harbour this worm. The face and palpi are yellow; the scutum black with yellow stripes; the abdomen yellow with a dusky brown tip. The legs are yellow, with dark tibiæ and tarsi. The distal half of the wing is smoky.
 - C. silacca (Austen) is a common species in West Africa, also an intermediary

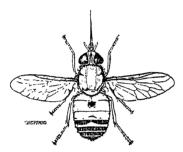




Fig. 378.—Chrysops dimidiata (v.d. Wulp.), $\varphi \times 2\frac{1}{2}$.

for Low low and is found infected with this filaria in the Cameroons. It differs from the former species in having a red or bright orange abdomen and legs with dark-brown tarsi. C. distinctipennis may transmit L. low in the Sudan.

FAMILY MUSCIDÆ1

Genus Glossina. (Wiedemann, 1830) "Tsetse Flies." (Plates IV, V)

These are large, but narrow-bodied flies, 6 to 14 mm. long, with a slender probose projecting forwards to twice the length of the head, enclosed in inwardly grooved palpi. The wings are long, clear to brownish, with the 4th longitudinal vein curved sharply forwards to meet a short transverse vein. This and the position of the wings at rest, overlapping on the back (Fig. 379) are characteristic of Glossina, distinguishing it from Stomorys (Fig. 382). Hamatopota or Chrysops. The body is dark brown or grey; the abdomen in some species is marked by well-defined dark brown cross bands, interrupted in the middle line, on a buff or grey ground. The proboscis consists of three parts, labrum, hypopharynx and labium (Fig. 380). The bulb of the labium contains muscles which activate a cutting mechanism at its tip. In feeding, the proboscis is inserted up to the bulb, and then withdrawn a little before sucking proceeds. The bite of larger species is exceedingly painful.

Tsetse flies are confined to tropical Africa. Records from the south-west corner of Arabia are doubtful. The two most important species, G. pulpalis

 $^{^1}$ The Editor is indebted to Dr. Kenneth Morris, D.Sc., F.R.E.S., for considerable assistance in this description of the tsetse flies.

G. and morsituns, together cover the greater part of equatorial Africa. The genus comprises twenty species, divided by Austen into four groups (see table facing p. 1052). Five species are definitely known to transmit sleeping sickness in the field; seven are concerned in the transmission of animal trypanosomiasis. Many can be shown to transmit various trypanosomes in the laboratory, but are unlikely to act as vectors in nature, because of their habits. To obtain blood the tip of the proboscis is flexed, which enables the blood to be sucked up by "pool-feeding." People become sensitized to these flies and the reaction is then intense with swelling and wheal formation in response to injection of the insect's saliva.

Bionomics.—These flies are adapted to certain conditions which vary with the species; some are just capable of surviving the unfavourable season and a comparatively small change may suffice to tip the balance against the fly, and even modifications in the vegetational cover are effective. Swynnerton laid

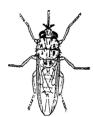


Fig. 379.—Tsetse fly at rest x about 11.

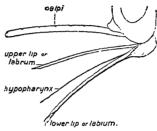


Fig. 380.—Mouth-parts of Glossina.

down that each species needs the concurrence of vegetational types which are necessary for mating, breeding, feeding and sheltering. Hungry flies haunt roads and pathways. They do not live in continued association with herds of game, but rather feed, then fly away to digest their meal. Each species has its own food preference. Their eyes are adapted for detection of movements as distinct from appreciation of form, but scent plays a part in the case of G. pallidipes, G. palpalis and G. brevipalpis. Testse flies are dispersed by spontaneous movements along paths and by carriage by cattle and game; there is also automatic dispersal as the result of seasonal expansion, the basis of which is hunger.

Life-history.—The larvæ mature one at a time in the abdomen nourished by secretion from the highly-branched milk glands which ramify throughout the abdomen. They remain in the uterus 10–12 days and, when fully developed, the female selects a suitable place to deposit them. The larva is therefore discharged fully-developed; when fully-grown it is almost as large as the abdomen of the female fly, and is a yellowish ovoid body composed of thirteen segments with two small hooks at the anterior pole and two respiratory protuberances at the posterior end (Fig. 381). It burrows half an inch into loose soil or sand, or conceals itself under dead leaves. Then it rounds itself up, hardens, and the chitinous covering becomes dark brown. After the pupal stage has lasted three to four weeks the fly emerges. The adult female lives 3–6 months, and during this period 6–12 larvæ are produced. A female tsetse deposits the larvæ singly, at intervals of about eight days, choosing a shaded spot, where cover for the pupating larvæ is available in the form of humus, for instance, beneath a log.

Technique of dissection of glossina.—The freshly-killed insect should be placed on a slide with the wings and legs removed. To demonstrate the salivary glands, the fly should be fastened to the floor of a dissecting trough and enough normal saline added to cover it.

Two incisions are then made in the thorax: (1) a median longitudinal from the neck to the end of the abdomen; (2) a transverse incision extending in a line with the bases of the wings, or along the transverse suture. The integument of the lateral walls is severed almost to a point near the attachment of the legs, care being taken not to cut too deeply into the muscular tissues.

A dissecting needle is inserted at either end of the longitudinal slit, and the thorax gently pulled asunder. The muscular tissues are teased out from the anterior half of the thorax and head, leaving the glands attached to the hypopharynx and the labium.

For the removal of the gut, the fly should be placed, vertical surface uppermost, on a glass slide and a drop or two of normal saline added. The integument



Fig. 381.—A, Larva of Glossina pakpalis. B, Puparium (After Roubaud.)



Fig. 382.—Stomoxys calcitrans. \times 3.

is gently nicked at the sides as near the end of the abdomen as possible. The left hand needle should be placed on the thorax, and the right hand one on the partly severed end of the abdomen. The latter should be gently pulled aside until all the viscera are dragged out.

Species.—The most important vectors of human trypanesomes are G. palpalis, G. morsitans, G. tachinoides and, to a lesser extent, G. brevipalpis and G. swynnertoni.

G. palpalis, Rob-Desv.—This has a very wide distribution, throughout West Africa from Gambia to the Congo and eastwards to Lake Victoria. It requires a high humidity (45 to 85 per cent. relative humidity), and temperature 21°-32° C. which, together with food, influence its distribution. It is not found in tropical rain forest except in clearings around villages, roads and farms, but usually lives close to water. In the savanna country (less than 50" rainfall) it requires the heavy shade found only along water courses. Seasonal distribution is pronounced; it is confined to dense evergreen shade and permanent water (primary foci) in the dry season, spreading widely in the rains to secondary foci of deciduous thickets. Breeding strictly follows this distribution, since exposure to sun or desiccation is fatal to the puparia. It is most partial to man and domestic animals, but also feeds on lizards, monitors, tortoises, crocodiles and hippopotami. These seem the main food hosts in West Africa, limiting the distribution to the neighbourhood of human habitations, whereas in East Africa it is able to subsist largely on wild mammalia and reptiles. On large rivers and lakes it constantly moves along the banks and will follow canoes far out, but on small streams or water-holes the fly populations are stationary and congregate around small glades or openings in the bush which constitute feeding grounds. Hence the danger of small clearings around water-holes, paths or villages, which

create artificial feeding grounds with maximum opportunities for transmission of trypanosomiasis. Its distribution and marked preference for human food make this species the most potent vector of Trypanosoma gambiense. In West Africa it transmits trypanosomiasis of stock also. The subspecies G. palpalis fuscipes (inland East Africa to Congo district and Cameroons) is found sometimes 12 miles from water in areas of humid forest interspersed with elephant tracks. It evinces great need for shade and high humidity. On Lake Victoria these flies are carried and dispersed by canoe traffic. The pupæ are deposited in shaded sand of the fly beaches, but during the dry season it contracts its range and may then die out spontaneously. Ssp. fuscipes is distinguished by special shape of the gonopods; ssp. martinii (Lake Tanganvika) likewisc.

G. austeni, Newst, 1912 (East African coastal district).—This species favours secondary thickets, especially on River Juba in Somaliland, which are more or less evergreen in the dry season. It breeds in fairly dense cover, but may do so in open vegetation and is usually found in miombo forest and thickets, from coast level to 3,000 ft. Reluctant to approach man, it feeds mostly on cattle, is active by night and is guided by scent.

G. lachinoides, Westw.—This is found in West Africa north of the coastal and forest zones, also in the south-west corner of Arabia. It requires slightly drier climatic conditions than G. palpalis, hence its distribution throughout inland savanna, where the primary (dry-season) foci are confined to evergreen bush fringing rivers and lakes with permanent water, from which there is a wet season extension of 5 to 6 miles to secondary foci along temporary streams or pools. It can breed in lighter bush than G. palpalis, but shade and proximity of water are essential. It is very catholic in its choice of host and is able to subsist entirely on reptilian blood. It does not form concentrations in the proximity of villages, as does G. palpalis, unless this is necessitated by limitations of suitable cover. It is an important vector of T. gambiense in the hinterland of West Africa, also of T. vivax and T. congolense among cattle.

G. morsitans, Westw.—This is widely distributed throughout equatorial Africa, from the Anglo-Egyptian Sudan to Rhodesia in the east, and from Senegal to the Congo in the west. In its western range it is represented by the geographical race or sub-species, G. morsitans submorsitans, Newst. It is essentially a tsetse of savanna, where it is widespread, irrespective of the presence of surface water. It is found from sea-level to 5,500 ft. in East Africa. Its climatic requirements are 40-60 per cont. relative humidity and a mean annual temperature of 21° C. It never occurs within evergreen or intermediate forest. Savanna woodland and thorn thickets (the Isoberlina-Brachystegia woodland, or "mionibo") form its breeding and resting places, and open grassland and glades between woodland are its feeding grounds. It is unable to live in thorn bush, except in regions of high rainfall, but in Ngamiland it prefers the thickest vegetational types, breeding taking place on forest fringes. The seasonal concentration of the fly into dry season foci is less marked in East than in West Africa, where the dry weather climate closely approaches conditions fatal to the fly. It is essentially a game tsetse, dependent on large ungulates for its main food supply, though attacking man and cattle readily when in contact with them. Within its climatic range, the presence and movement of fly concentrations is governed by those of game. The feeding grounds are small glades or edges of open spaces and its breeding haunts are beneath fallen logs, in hollows between root bases of trees, in rot holes and other dark places. The females travel through savanna more extensively than do the males. The latter seldom live longer than 2-6 weeks; the former twice as long. Moreover the female population is twice as great and they attack man when fly density is at its lowest ebb. Both races, G. morsitans and G. submersitans, disperse when rains commence, but the longer rainy season in Tanganyika results in much more extensive dispersal than occurs in Nigeria. It tends especially to attack moving objects, following game, cattle or humans for miles. This, and its habit of entering cars or trains passing through a fly-belt, brings the fly into towns and villages, and also causes spread into new districts, though it is not partial to human blood. The increase and spread of *G. morsitans* is alarming in many parts of East Africa and has caused wide desolation through loss of cattle: 200,000 sq. miles of Tanganyika have been rendered unproductive through the presence of this and the following two species. Its spread is one of the main agricultural problems of Tanganyika, Nyasaland and Northern Rhodesia. It carries Trypanosoma rhodesiense, cattle and game trypanosomes, especially T. brucei.

G. suynnertoni, Austen.—This has a local distribution in Tanganyika and just into Kenya, but is of considerable importance as a vector of trypanosomes of both man (T. rhodesiense) and cattle. It was involved in an outbreak of sleeping sickness in Mwanza Province, Tanganyika (see p. 133). A savanna testse and a game feeder (the main food hosts are kudu, roan antelope, giraffe and pig), it yet freely attacks man, domestic animals, monkeys and rodents, and so cannoble controlled by game cradication. It is said to be the only species which is found in houses. It is found up to 6,000 ft. and breeds mainly in thickets with a rainfall of 16–30 in. This species is readily controlled by applications of gammexane at 14-day intervals.

d. pallidipes, Austen.-- This has a wide distribution in East Africa, Italian Somaliland, Uganda, Kenya, Tanganyika, Nyasaland, Northern Rhodesia and Zululand. It requires a slightly higher humidity than d. marsitans, and occupies dense savanna forest and secondary forest. It is a game feeder and an important vector of cattle trypanosomes. Its presence renders useless 1,250 sq. miles of fertile grazing in the Masai reserve and 3,000 sq. miles, or half the territory, in Zululand. It is found up to 6,000 ft. Humidity is a factor in the activity of this fly.

d. longipalpis, Wied.—This is the West African representative of d. pallidipes, occurring from Senegal to the Cameroons, in secondary forest, coastal savanna and dense savanna forest inland. It does not enter tropical rain forest. It subsists mainly on smaller antelopes, and is a vector of cattle trypanosomes. It has occasionally been found naturally infected with T. gambiense.

d. brevipalpis, Newst.—This has a wide distribution from Abyssinia to Zululand and westwards to the Belgian Congo, and a similar habitat to *d. palpalis*, in gallery forest and dense secondary forest, but it can stand slightly drier conditions. It lives on mammalian hosts, and frequently attacks man, cattle and pigs. It may transmit both sleeping sickness (*T. gambiense*) and nagana (*T. brucei*).

G. longipennis, Corti.—This is found throughout the dry savanna and thorny scrub belt of East Africa, from the Southern Sudan and Italian Somaliland, through Kenya to Tanganyika. It is not known to have been associated with any outbreaks of human or animal trypanosomiasis.

G. fusca, Walk.—This is confined to forest regions of West Africa. Its activity is crepuscular, with a preference for horses and cattle rather than man. It has been found infected with the trypanosomes of nagana (T. brucci).

G. fuscipleuris, Austen.—This is the East African representative of U. fusca, occurring in forest and gallery forest of the Eastern Belgian Congo and country around Lake Victoria. It tends to attack man and domestic stock, and is known as a plague in the Masai reserve through its exceedingly painful bite which stampedes cattle. It transmits nagana (T. brucei).

G. pallicera, Bigot.—This is distributed fairly widely through West African rain forest. It rarely bites man, so is little noticed and unlikely to be involved in the transmission of human trypanosomiasis.

Control measures.—Early diagnosis and treatment of cases of sleeping sickness are essential, and especially "mass treatment" by mobile teams, examining and treating the total population, village by village, but mass treatment alone, without simultaneous entomological measures, has, as in French West Africa, failed to eradicate sleeping sickness.

Entomological.—The only effective measure, so far devised, is an alteration of habitat by clearing. Two types are used: (1) eradicative, aims at extermination of the complete fly community by removing essential plant associations of all primary foci over a large district; (2) protective, to reduce contact between fly and man by removing all fly-belt vegetation from around villages, road and river crossings, water-holes, etc. A minimum of 440 yards on each side of the object is considered necessary for G. palpalis and G. tachinoides, but this method is useless against G. morsitans group. Protective clearing at best is an unsatisfactory palliative and is apt to go wrong, whilst bad clearing may make the conditions worse than before. Before clearing it is essential to have accurate knowledge of the species of glossina involved and its exact habitat, and a detailed study of the botany of the fly-belt now shows that the fly can be exterminated by removal of a few definite species of tree.

The preparation for this kind of work consists of a vegetational, agricultural and tsetse survey and selection of lines for isolation barriers to enclose blocks of tsetse-infected bush and should consist of (a) naturally open spaces, (b) bush-types sufficiently wide, unsuited for the tsetse concerned, (c) continuous wide thicket for G. morsitans and G. surunnertoni.

In East Africa the four important species to be guarded against are: G. morsitans, G. swynnertoni, G. pallidipes and G. palpalis.

The presence of man appears to repell *G. morsitans*. Great advances have been made in the methods of reclaiming land, especially in Tanganyika. In order to convert fly-bush to cultivation steppe definite lines should be made in which the bush is cut back and cleared. In thorn savanna infested with *G. swynnertoni*, discriminative clearing is satisfactory, but in plains adorned with lace-work of vegetation infested with *G. swynnertoni* and *G. morsitans*, a clearing of one mile wide should be made along the edge of the thorn bush. By these methods during the last twenty years some 1,000 square miles of Tanganyika have been freed from tsetse. (Nevertheless two-thirds to three-quarters of the land is still infested. In Kenya the figure is about one-seventh and in Uganda one-fifth.) For the results of DDT, see p. 865.

Traps.—Harris claimed considerable success in Zululand with a tsetse fly trap, the material for which costs about 30 shillings. This is designed to resemble a cow or antelope and consists of a framework of light wood, covered by hessian cloth roughly triangular in section, with a flat top, 6 ft. long by 3 ft. wide, the sides converging to about 3 in. apart, with a narrow open slit at the bottom, the ends being vertical and triangular. The body is slung on wires, so that the open slit is 48 in. from the ground. To the flat upper surface a transparent cage of wire gauze, of a mesh sufficient to retain a fly, is fixed.

Where the cage fits to the flat surface, the cloth is removed and the wire so arranged that the flies cannot return to the hollow body of the trap.

These traps are then suspended on the sunny margins of evergreen bush haunts of the flies, and so placed that they throw a separate shadow, and it has been found that, in suitable weather, each trap will kill 100–200 flies daily. This type has been successful with G. pallidipes and G. palpalis, but is not so with G. morsitans. The single screen (S.S.) trap is excellent for G. palpalis and G. pallidipes, and where suitable climatic conditions prevail, G. morsitans is attracted, but these traps have been found useless in Southern Rhodesia.

Swynnerton employed a similar trap, containing a live calf, to which the

lies are attracted by scent. The most effective is a moving screen carried by ly-boys, who are able to catch with a net every fly that the screen attracts. Hand catching is effective in small isolated fly-belts. Tanglefoot spread on clothes or on shields or screens protects labourers from being bitten. An attempt to introduce a sterile race of testes has been made by Vanderplank, who crossed *G. morsitans* with *G. swynnertoni*, and the cross-mating produced fewer pupe. The male hybrid inseminate females, but there have been no offspring, whilst attempts to cross female hybrids with pure-bred males of both species have failed.

In West Africa operations have been directed against *G. pulpalis* and *G. tuchinoides*, but the most important is connected with the Anchau settlement in Nigeria. This has entailed surveys, the construction of roads, clearing 110 miles of stream, sinking of wells, study of local soils and vegetation, agricultural experiments, investigation of native farming methods, census, monthly fly surveys, and construction of new settlements. Two other campaigns of protective clearing have been carried out in Nigeria in 1938 in Katsina and Zaria.

By these means it is estimated that 200,000 people have been protected against infection. Large-scale experiments in eradication of these two species from the savanna forest of the northern territories of the Gold Coast are also in hand. Removal of trees and shrubs concerned throughout the whole river system has resulted in the disappearance of these flies, especially in the Lawra district in the northern territory drained by the Kamba river.

"Rod clearings," in the West Nile district of Uganda especially, are used for the control of G. palpalis fuscipes, extend 10 yards in width on either side of the river and project 800 yards in length, with the village or road crossing in the centre. The grass is kept short.

Gruss-firing.—Nash advises against this measure which is commonly practised in the dry season as favouring the spread of tsetse. Prohibition has resulted in the reduction of the *G. morsitans* population in Tanganyika, which may be due to the destruction of pupe by ants.

In Northern Nigeria climatic conditions are so severe that destruction of woodland by fire exclusively reduces shelter needed by *G. morsitans*, but there is no evidence that it diminishes the *G. pallidipes* population.

Barriers.—Thickets of the Burtia-Baphia type may be dense enough to form an effective barrier against G. swynnertoni as these flies will not cross them, but they need to be more than one mile wide to prevent them from drifting through during the leafless season.

Afforestation with evergreen thicket, as on the edge of a deciduous barrier, can be considered as a measure against the advance of *G. morsitans*.

In Tanganyika it has been shown that a thicket barrier consisting largely of Euphorbia terucalli, 100 yards deep, impedes the passage of G. swunnertoni.

Symes's block method is mainly devised for G. palpalis. Blocks of riverine bush, about two miles in length, are separated by clearings made 1,000 yards wide. Paths are made along the river banks and these are patrolled by catchers with nets. In one block hand-catching reduced the numbers caught from over 5,000 in three months to seven in five months in 1935. Along the shores of Lake Victoria the block method, combined with hand-catching, has been instrumental in reclaiming 16 square miles of land, and similar methods have been successful along the rivers in Kenya and S. Sudan.

Game control.—The arguments in favour of control by killing off game came chiefly from Rhodesia and Bechuanaland, where G. morsitans is concerned. It is claimed that anti-tsetse measures should include game control, not to the limit of extermination, but by rigid control. Buffalo and wildebeeste should be declared vermin. In Southern Rhodesia it is claimed that effectiveness is

established on these lines: (1) reduction of game along the edge of fly-free country; (2) creation of a game-free zone, 10 miles or more wide, beyond farm boundaries; (3) control of motor traffic, of hunters and prospectors. By these measures in 1940 and 1941, 36,000 wild animals were shot and the position was greatly improved.

From French West Africa come arguments against game destruction. There is no evidence that big game, in a wide sense, can be reservoirs of *T. gambiense*,

and at best constitute only a minor reservoir for T. rhodesiense.

Social.—Segregation of infected people and movement of the population out of infected areas may be used as a last resort in severe outbreaks, or where other control measures are impracticable. Control of travellers passing through sleeping-sickness zones must be instituted. The spread of the morsitans group of flies has been prevented by passing traffic through a cleaning chamber on leaving a fly-belt. Re-population and development of cleared areas inhibits re-growth of fly-belt vegetation and re-entry of the fly. Siting new villages at primary foci of the game tsetse, after initial measures against the fly, has successfully broken up large fly communities.



Fig. 383.—Musca domestica, $\circ \times 4$.

MUSCIDÆ THAT DO NOT SUCK BLOOD

The common housefly (Fig. 383), Musca domestica, is a domestic species; on account of its insanitary habits it acts as a vector of pathogenic microorganisms, especially dysentery bacilli, cysts of Entamæba histolytica, other intestinal protozoa and helminth eggs.

M. domestica (8 mm. in length) is dark grey, with four parallel black stripes on the dorsum of the thorax. Eggs are laid in masses in manure and other refuse, hatching in twenty-four hours in hot weather. The larvæ are legless maggots with large stigmal plates, bearing posterior spiracles on the abdomen. Pupation under favourable conditions occurs in five days. The puparium is an elongated barrel shape, and in the tropics the pupal stage lasts three days. The adult fly lives about one month. Larvæ are capable of traversing considerable thicknesses —over 3 feet—of soil in order to reach the surface. In the tropics houseflies are in evidence throughout the year; in dry deserts they die off during the hot season. In temperate zones they perish in the winter season, but are most numerous in the early autumn. Larvæ survive the winter buried in decaying vegetable matter. The best method of storing manure is to ram it so tight that fermentation is intense enough to destroy maggots.

The nematode worm, Habronema musca (stomach-worm of horses), is ingested by M. domestica in its egg or larval stage, and the embryo continues its development in the body of the fly, so that the final stage is found in the proboscis of this insect.

SARCOPHAGIDÆ (Flesh flies)

"Blowflies" include blue-bottles, green-bottles ($Calliphorid\alpha$) and flesh flies ($Sarcophagid\alpha$). The larvæ usually feed on dead animals. These flies are primarily scavengers.

Wohlfahrtia magnifica (Schiner, 1862), the principal sheep-maggot of South Europe, measures 10-13 mm., and is ashy-grey, with black legs. The abdomen is light-grey with three black spots on each segment. This species is found in Russia, and thence to Egypt and Asia Minor. In man, larvæ are found in open wounds, nasal fossæ, palate and eyes (see p. 843). The larvæ of these various muscid flies are identified by the shape of the posterior stigmata. (Fig. 384.)

Chrysomyia bezziana (Villeneuve, 1914) is metallic blue with a bright-green thorax. The male has reddish-brown eyes closely approximated, and deep orange antennæ. The larva (12 mm.) is yellowish-white, with slightly pigmented extremities. Eggs are laid in diseased tissues whilst larvæ in wounds cause great destruction of tissues in India and Cochin-China.

Cochliomyia¹ hominivorax (Coq., 1858), syn. C. americana (Fig. 385), the "screwworm" fly, is common throughout America as an obligatory flesh-breeding fly.

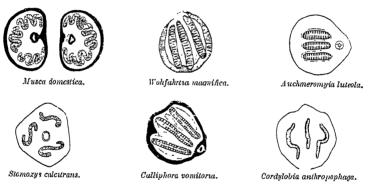


Fig. 384.—Stigmata of muscid larvæ, a means of rapid identification.

Magnified.

It was originally thought to be the same as C. macellaria, which is essentially a carcass-breeder. It is greyish, with three well-marked dorsal stripes, and measures 9-10 mm. It lays masses (300-400) of eggs on the surface of wounds, in ears and nasal fossæ, and from there larvæ are hatched in a few hours. The larva (Fig. 386) is white, $\frac{3}{4}$ in. in length, and formed of twelve segments, with circles of minute spirally-arranged spines giving it a screw-like appearance. The larvæ burrow into tissues, destroying cartilage and bone. Ear or nasal fossæ may be attacked, and the brain may be penetrated, causing death.

Cordylobia anthropophaga (Grünberg, 1903) (Fig. 387), the Tumbu Fly or "Ver du Cayor," is widely spread in Central Africa. It measures 8.5 to 11.5 mm., and is yellowish-grey, with black spots on the abdomen and brown wings, and resembles Auchmeromyia luteola. The male Cordylobia is distinguished from the male of A. luteola by its closely-set eyes. In the female Cordylobia the abdominal segments are of equal size, while the female Auchmeromyia has a triangular abdomen with the second segment long. They differ in life history and habits. Cordylobia is an obligatory myiasis producer and gives rise to

¹ Generic name—Calluroga is recognized by some entomologists.

lesions in man or animals. Usually, it is inactive; when disturbed, it flies away with great rapidity. The eggs, white and visible to the naked eye, are laid on the ground. or on clothing if it is contaminated by urine or sweat. Larvæ are

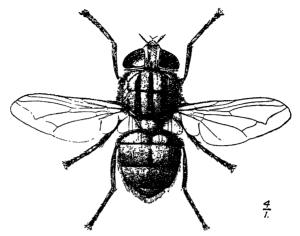


Fig. 385.—Cochliomyia hominivorax, female.

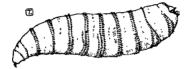


Fig. 386.—Cochliomyia hominivorax, larva. × 5.

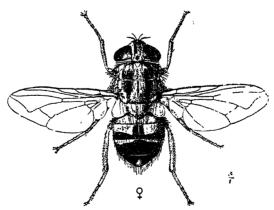


Fig. 387.—Cordylobia anthropophaga.

activated by the warm body of the host, and in the early stages are provided with structures, such as cuticular spines to assist penetration of the skin. There are three moults or instars (Fig. 388). Development in subcutaneous tissues is completed in twelve days. The cavity containing the larvæ breaks down to

form a swelling, resembling a boil which bursts without much inflammation. The larvæ emerge from the swellings (Fig. 208, p. 841), which are situated on the forearm, scrotum, and other parts of the body; they fall to the ground and pupate in thirty-six hours. The pupa has a characteristic shape with a square truncated extremity. Pupal cases are commonly found in rat holes. The adult hatches in 10–20 days according to the temperature prevailing.

Larvæ can be extracted by pouring water over the hole in the skin, thus stopping their oxygen supply; they then extend their posterior spiracles, and

can be squeezed out.

The larvæ are generally found in densely shaded streams where the course is impeded by vegetation and the bottom is covered by decaying leaves, overlaid by fine sand.

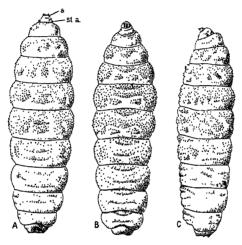


Fig. 388.—Adult larva of Cordylobia anthropophaga. × 5. (After Brumpt.)

A, Dorsal view; B, ventral view; C, lateral view. a, Antennæ; st.a., anterior spiracle.

The adult flies bite chiefly between 8.30 a.m. and 5 p.m. They seldom enter houses. They feed on the pool of blood which collects when the tissues are lacerated by the proboscis; 18-40 c.mm. are taken at one meal. They probably feed about once a fortnight (Gordon).

The Tumbu fly provides a remarkable example of metazoan immunity. In guinea-pigs the degree of immunity produced by previous infection is not general, but local. No antibodies are present in the serum. Larvæ penetrating into the immune area die in forty hours, while immune skin grafted on a non-immune

animal retains and imparts its immunity (Blacklock and Gordon).

Auchmeromyia luteola (Fabr., 1805) (Fig. 389) is widely distributed throughout tropical Africa, from Northern Nigeria to Natal, and also in Southern Sudan, in latitudes from 18° N. to 26° S. from sea level to 7,500 feet in dry or wet climates. Its general colour is orange-buff, but numerous small black hairs impart a smoky appearance. It measures 10–12 mm. with a stoutly-built body. The head is large, with the eyes well separated in both sexes. The thorax shows two indistinct, dark, longitudinal stripes. The abdomen differs in the sexes, the second segment in the female being twice the length of the same segment in the

male. In the female the dark band on the second segment is so wide that it occupies almost the whole. The third segment is almost black in both sexes. The wings are smoky-brown with conspicuous venation. Human and simian fæces constitute the most important source of food. First batch of eggs is laid 2–3 weeks after emergence. The larva (Fig. 390), known as the "Congo floormaggot," is dirty white, semi-transparent, 15 mm. in length, and composed of

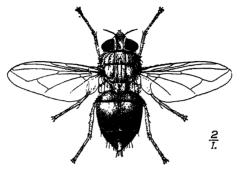


Fig. 389.—Auchmeromyia luteola, female.

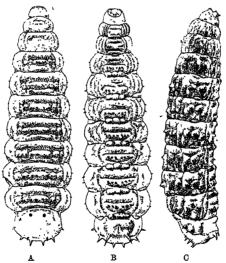


Fig. 390.—Larva of Auchmeromyia luteola. × 5. (After Brumpt.)

A, Dorsal view; B, ventral view; C, lateral view.

11 segments. The central part of its ventral surface is flattened. At the posterior margin of each segment are three short limbs, transversely arranged, provided with backwardly directed spines which enable the maggot to move about like a caterpillar. The anterior segment is roughly conical and bears a mouth which is placed between two black hooks protruding from the apex and curving backwards towards the ventral surface. Paired groups of minute teeth are placed around two hooks, forming a sort of cupping apparatus. There is a remarkable

dorsal diverticulum, corresponding to the food reservoir of the muscid larva which

opens into the œsophagus near the anterior end.

After the larva has fed it forms a conspicuous red object filled with blood. After taking its meal it retreats into the cracks in the floor from which it emerged. It feeds by scraping with the mouth-hooks until it reaches a blood-vessel. The first segment is then retracted and the sucker apparatus applied as in wetcupping. The host must be hairless and remain quiet, e.g., a man asleep. It also attacks the ardvark (anteater) and nestling birds. Larvæ are frequently found under the mats on which natives sleep and in the earth at a depth of 3 in. They feed mainly at night, and drop off at once, if disturbed. They can be recognized by the characteristic shape of the stigmata or openings of the respiratory tubes (Fig. 384).

When ready to pupate, the larva selects a suitable spot, and lies dormant. The puparium is a dark, reddish-brown, oblong body, 9-10.5 mm. by 4.5 mm.

This stage lasts from two to three weeks.

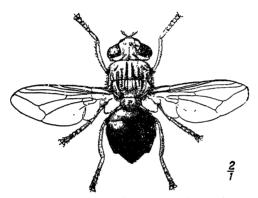


Fig. 391.—Dermatobia cyaniventris, female.

The adult fly (Fig. 387) is usually found sitting motionless amongst the thatch, beams and cobwebs of the walls and roofs of native huts and, on account of its protective coloration, is difficult to detect. It never bites, but deposits its eggs in the crevices of the floor, particularly mud-floors, in spots where urine has been voided. To avoid being bitten, travellers should sleep on beds or in hammocks. Bites are painless.

CHLOROPIDÆ

These are Hippelates flies, members of the family Chloropidæ (Oscinidæ) and commonly known as "frit flies." Small members are known as "eye flies" because of their liking for the lacrymal and sebaceous secretions, and also for blood and pus. They are extraordinarily persistent in their attentions.

Siphunculina funicola, the "eye fly" of India, Ceylon and Java, is responsible for the spread of conjunctivitis. It has been shown by Roy that the seasonal prevalence of this fly in Assam closely coincides with that of epidemic conjunctivitis, and there is a similar belief for an allied species in Southern United States. In parts of California these flies are a veritable pest.

Hippelates papillipes has been suspected of transmitting yaws in Jamaica (p. 602). They are small black flies with aristate antennæ. The eggs are deposited on decaying organic matter and the larvæ feed on the same material.

H. pusio, known as the "eye gnat," or "mal de ojo," is particularly abundant in Florida and causes great annovance to men and animals.

OESTRIDÆ (Bot-Flies)

These are non-blood-sucking flies with primitive mouth-parts, parasitic on animals and man during their larval stages. Cases of ophthalmomyiasis of man have been ascribed to the larvæ of head maggots of sheep and deer. Cases traceable to *Oestrus ovis* and *Rhinæstrus purpureus* have been reported (p. 843).

Dermatobia cyaniventris (Macquart, 1843) (Fig. 391), "ver macaque" or



Fig. 392. — Dermatobia cyaniventris larva: early stage. (Blanchard.)

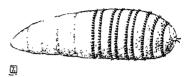


Fig. 393.—Dermatobia cyaniventris larva: later stage. (After Brauer.)

"macaw-worm," is widely distributed throughout South America. The larva occurs in the most diverse animals: cattle, pigs, dogs, agouti, jaguar, South American monkeys and birds; it is rare in the mule and never found in the horse. It can complete its development in man and is an example of "obligatory cutaneous myiasis." In man it is found in the head, arm, back, abdomen, thigh and axilla. When the larvæ are hatched out they penetrate the skin and produce an inflamed swelling about the aperture of entrance, from which exudes a sero-purulent fluid containing the dark fæces of the larvæ. At an early stage the larva has the curious appearance depicted (Fig. 392) and is known as "ver macaque"; and later, when larger (Fig. 393), it is called torcel or berne. This

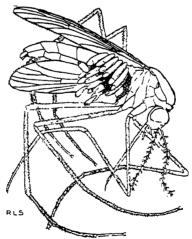


Fig. 394.—Psorophora (Janthinosoma) lutzi, carrying eggs of D. cyaniventris.
(By courtesy of Tropical Diseases Bureau.)

myiasis is acquired in a curious manner. On attaining maturity, D. cyaniventris lays eggs on wet leaves in damp places where mosquitoes feed, especially Psorophora (Janthinosoma) lutzi (Fig. 394). Other species can take on this function:—mosquitoes: Psorophora posticata, P. tovari and Gældia longipes; flies: Sarcophaga terminalis, Musca domestica, Stomoxys calcitrans; and a tick,

Amblyomma cajennense. Packets of eggs are enclosed in a cement which, becoming softened by moisture, adheres to the insect's thorax, and the eggs are thus conveyed to man or other vertebrates when the mosquito next feeds. This process is known as "phoresy" or hitch-hiking. The eggs develop, and the larvæ, attracted by warmth when the insect feeds, burrow into the skin and develop like cordylobia.

Hypoderma, the cattlegrub, or "ox warble," has the ox as its normal host; man is very occasionally parasitized, producing "larva migrans" (p. 845). Two well-known species are H. lineata and H. bovis, 13-15 mm., widely distributed in Europe, Asia and North America. The eggs of both species are deposited on the hairs of cattle, hatching within a week. Small larvæ then crawl down the hairs and bore into the skin.

Horse bot-flies, Gastrophilus, especially G. hæmorrhoidalis, sometimes attack man, the larvæ burrowing under the skin, causing a creeping eruption. Larvæ are picked up by handling horses, though there is evidence that the fly can actually introduce its eggs directly under the skin. These flies are somewhat smaller than honey bees, with small antennæ sunken in pits. They are strong fliers. Larvæ live in the stomach and intestines of horses. Eggs are deposited on hairs.

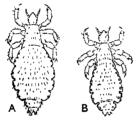


Fig. 395.—Pediculus humanus. × 5. (After Bruce Cummings; by permission of Trustees of Brit. Mus.)

A, P. humanus, Q.
B, P. humanus var. capitis, Q.



Fig. 396. — Phthirus pubis, φ, showing contained ovum. × 12.

ANOPLURA (LICE)

Lice are obligatory parasites and spend the whole of their life on the body of some particular host. They cannot live, apart from their host, longer than 12 hours at 40° C. or 10 days at 5° C. There is a great reduction in the size of the eyes and antennæ. They have flattened bodies without wings, and an indistinctly segmented thorax. The integument is tough, to resist pressure. The number of abdominal segments ranges from six to nine, the last being bilobed. Spiracles stand out prominently on the sides of the abdominal segments. In the male the abdomen ends bluntly, bearing a spine-like penis. The legs are modified for holding on. The eggs, or nits, adhere to the body hairs of host, and the young which emerge are miniature editions of the adults. The species of louse parasitic on man is Pediculus humanus of which there are two races, the headlouse, P. capitis, and the body-louse, P. corporis (Fig. 396). These interbreed and produce fertile offspring. The egg nits of P. corporis are laid on the body hair, but mostly on the inner surface of clothing. Those of P. capitis are laid on the head at the base of the hairs, which grow up with them. The female produces about five eggs a day and continues to do so for a month; the eggs hatch in eight days at 32° C., but take longer at a lower temperature. The

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immature louse, or nymph, moults three times, and becomes mature in fourteen days. Like the adult, it feeds on blood twice a day. The life span of the adult is from four to six weeks. Lice cannot live for any length of time on discarded clothing. Under experimental conditions they can survive at the low temperature of 5° C.

Infection with lice occurs through close contact with verminous persons huddled together. Lice avoid light, and tend to leave patients with fever and sweating, so that this is a factor in the transmission of disease. They also leave a body which is undergoing hard physical exercise.

Lice convey relapsing fever and the rickettsia of exanthemic typhus (R. prowazeki), and that of trench fever (R. quintana). They also play a part in the spread of tæniasis. Dipyllidium caninum is occasionally found in children and has as its larval host Trichodectes canis, the dog louse, and it may also develop in P. humanus.

The third species is *Phthirus pubis* (Fig. 396), the "crab-louse," which lives chiefly in the genital and inguinal regions, and is acquired mostly during coitus. It is distinguished from other lice by its broad flat body and festooned abdomen of six segments. The second and third pairs of legs have massive talon-like claws. By these means the louse clings to two approximated hairs 2 mm. apart. The life cycle is completed in 27 days.

The lice of rats and pigs—Hæmatopinus and Polyplax—also belong to this family.

Prophylaxis.—For destruction of lice in clothes on a large scale the most efficient method is by dry or moist heat; a temperature of 50–55° C. will kill in forty minutes. The application of a hot iron to the seams is useful. For practical purposes, clothes should be exposed to 70° C. for thirty minutes. Attention must be directed to folds and pleats.

For head lice the hair must be cut short, and a comb with square-edged teeth (Sacker patent), used with soft soap, is useful to remove nits. For destruction of adult lice all former methods have now been superseded by DDT or "neocid," and for details Chapter LII, p. 861, should be consulted.

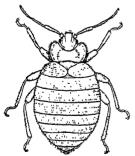


Fig. 397.—Cimex lectularius × 7.

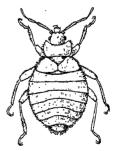


Fig. 398. — Cimex hemiptera (rotundatus). × 6.

HEMIPTERA (BUGS)

Bed-bugs (Cimex) have a world-wide distribution. The species parasitic on man are Cimex lectularius (Fig. 397), the bed-bug of Europe, and C. hemiptera (rotundatus), the bug of the tropics, which is distinguished by its elongated, narrow

abdomen (Fig. 398). In West Africa a species of another genus—Leptocimex boueti—attacks man. The body of C. lectularius is broad and flat, the head short and broad, attached to the thorax, the antennæ four-jointed, and the eyes present, but reduced in size. The mouth parts (jointed proboscis) are normally folded back under the head. The maxillæ are serrated at the tip. Lying in a groove between the head and the thorax are short pad-like hemi-elytra characteristic of the practically wingless condition. Cimex feeds only on blood, and can resist starvation well. The labium does not pierce the skin, but buckles up like that of a mosquito. The bodies of bugs give out a nasty, pungent odour. Bed-bugs are nocturnal in their feeding habits, hiding in crevices during the day-time. The eggs are shaped like a wine-bottle with a cap, and stuck on to the surface of the crevices of woodwork in houses, beds, mattresses, behind pictures and nail holes. Nests can be located by finding the black fæces round holes.

The females deposit eggs in batches from 10 to 50, totalling 200–500: they are large, yellowish-white, and easily visible to the naked eye. The nymphs resemble adults, and are white, with no elytra or rudimentary wings; they mature in about six weeks, if fed at each stage, but each can resist starvation for two months. Under less favourable conditions, development may be protracted to six months or more. Adults may live for many months. Bed-bugs are sensitive to high temperatures: even 100° F. with a fairly high humidity will kill many. The most effective method is fumigation with sulphur. The dosage necessary varies from 12–26 ounces per 1,000 cubic feet, with an exposure of at least six hours. Sulphur dioxide is cheap and, owing to its smell, free from hazard. It kills the active stages of the bug, but a few eggs may escape, and complete combustion must be ensured.

Hydrocyanic-acid fumigation is very efficacious, but dangerous, and must be carried out only by skilled persons. For articles of furniture, which cannot be boiled in water, an emulsion of petroleum is used: 3 parts of soap to 15 of hot water, to which 70–100 parts of oil are added, should be forced into cracks and crevices with a brush.

Coal-tar naphtha is lethal to bugs and nymphs, but less so to eggs. The concentration which can be obtained at 60° F. is 0·2 per cent. over a period of twenty-four hours. Bugs are also readily destroyed by DDT (see p. 865).

Though bed-bugs cause a great deal of irritation by their bites, they have not been actually proved to disseminate disease, with the doubtful exception of relapsing fever, as the experiments of Rosenholz (1927) seemed to show.

Reduviid bugs include a number of species which feed on human blood, inflicting painful bites. They are classified into four families—Panstrongylus, Eratyrus, Triatoma, and Rhodnius, and are confined to America, from 41° N. to 41° S. One (T. rubrofasciata) has a cosmopolitan distribution.

Those bugs live entirely on wild animals in nests and burrows, but certain species become domesticated. Larvæ and nymphs are flightless, and can only bite human beings in their immediate vicinity, but the adults of both sexes can fly considerable distances. When engorged with blood after a feed they void from the cloaca into the bite a white of dark fluid. This is probably how Trypanosoma cruzi is transmitted. Eggs are laid singly.

The larvæ, on emerging, engorge themselves with blood on four occasions, undergoing a moult after each; they then become nymphs, which, after several feeds. moult for a fifth and final time before becoming adult. The whole cycle of evolution takes three or four months to complete.

The life-span is on an average one of three months, and when once infected with *T. cruzi* the insects remain so for the remainder of their life span.

PANSTRONGYLUS (Burmeister, 1835) AND TRIATOMA (Wolf, 1802)

The genera Pansirongulus and Triatoma were separated by C. Pinto (1931) on certain characteristics of the probosces and antennæ.

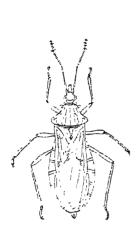


Fig. 399.—Panstrongylus megistus. Nat. size.

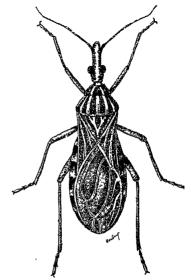


Fig. 400.—Rhodnius prolixus, adult male. \times 2\frac{1}{2}. (After Brumpt.)

Synonym.—Conorhinus (Laporte, 1832).

This genus is distinguished by its smooth body and elongated or conical head.

P. megustus (Burmeister, 1835)—Brazil—is a domestic species measuring 3 cm. in length. The body is black, with red stripes. (Fig. 399.) The insect has feeble powers of flight. The life-cycle takes a year to complete, and the adults can live about six months.

P. chagast (Brumpt and F. Gomes, 1914)—Brazil—has a characteristic red band on the head, and lives in the burrows of Kerodon rupestris and those of armadullos. This species has been found infected with Typunosoma cruzi at a considerable distance from human habitations.

P. dundlatus (Erichson, 1848)—Brazil, Venezuela, British Guiann, and San Salvador—is also naturally infected with T. ruzi and possibly conveys the human disease in San Salvador. P. genicultus (Lateille, 1811)—Paraguay, Brazil, Peru, Venezuela, and French Guiana—is a sombre-coloured species, living normally in armadillo burrows; it transmits T. ruzi to these animals.

Trutoma infestans (Kluz, 1834)—South America—is a domestic species and lives in cracks in the walls of houses or hen-roosts. It is found naturally infected with T. crusi in Argentina.

T. protracta (Uhler, 1894)—the United States, from Utah to California—is known as the "kissing bug," and lives in the burrows of rodents. Under natural conditions it harbours a trypanosome, T. neotomæ.

T. rubrofusciata (de Geer, 1773), a cosmopolitan domestic species, can be infected experimentally with T. cruzi. It has been suspected, on rather imperfect evidence, of once transmitting kala-azar in India. T. sunguisung (Lecomte, 1855)—United States—is a common domestic species which associates with

bed-bugs. Under experimental conditions it can be infected with T. cruzi. Dec-bugs. Conder experimental continuous it can be infected with 1. o acc.
T. sordida (Stal, 1859)—Brazil, Bolivia, and Paraguay—is a small domestic species met with near the banks of the large rivers; it has been found naturally infected with T. cruzi.
T. vitticeps (Stal, 1859)—Brazil—is the largest known of these insects, and is a rare species.

GENUS ERATYRUS (Stal)

Eratyrus cuspidatus (Stal, 1859)—Venezuela—is rare, occurs at an altitude of 4,600 feet, and is naturally infected with T. cruzi.

GENUS RHODNIUS (Stal, 1850)

This genus is characterized by a narrow attenuated head and by elongated antennæ (Fig. 400). Rholnius prolivus (Stal, 1859)—Venezuela, Colombia, Guiana, Brazil, and San Salvador. This species has nocturnal habits, and feeds voraciously on human blood. Normally it lives in the burrows of the armadillo and those of a rodent (Ca logenys subniger).

The adult is capable of flying considerable distances; the larvæ and nymphs live in cracks in the walls

and in the crevices of palm trees.

Under experimental conditions this species can transmit T. cruzi, and harbours T. rangeli (Pifano and Mayer, see p. 909).

SIPHONAPTERA (FLEAS)

Fleas have laterally compressed bodies and are wingless, with mouth parts adapted for piercing and sucking blood. They are active ecto-parasites, almost exclusively of birds and mammals, and do not resist starvation. Many are moderately specific in their choice of host, but will migrate to another where necessary. The female is larger than the male, and in the latter the curved receptaculum seminis forms a conspicuous feature. The eyes and antennæ are reduced, the latter fitting into a pit on the side of the head. The maxillæ are short and the mandibles function as cutting organs. Some have combs on the head and thorax. The body is contained in plates which represent a fusion of sternal, pleural and tergal portions. The ninth sternite is converted into a paired boomerang-shaped structure, and superficially looks like a clasper. White eggs are dropped by the female indiscriminately and hatch in summertime in three or four days. The larva lives in dust, feeds on débris, crumbs and fæces of adults, and is an active, footless maggot of a whitish colour, sparsely adorned with hairs (Fig. 401). When fully-grown, it spins a cocoon and pupates; the duration of this stage depends on temperature. A resting larval stage occurs, in which



Fig. 401.—Larva of Xenopsylla cheopis. Magnified. (After Bacot and Ridgway, "Parasitology.")

it can remain dormant for months. The pupæ are similar in shape to the adults, and encased in a cocoon. The adult may remain thus encased as a resting adult stage or *hypopus*. Resting adults are probably aroused by vibrations in empty houses which have become re-inhabited. Inside the crop, or proventriculus, there is a patch of spines, about eight hundred in number, which help to crush up the red blood corpuscles of the host.

There are two main families:—Pulicidæ (ordinary fleas), thirty genera, and

Tungidæ (chiggers), a small group.

Of Pulicida five genera are important, and the following points are used for identification:—

1. Head and thorax without combs—Pulex or Xenopsylla.

2. Head, no comb; thorax with combs—Nosopsyllus (Ceratophyllus).

3. Head and thorax with comb—Ctenocephalides (Ctenocephalus).

4. Head pointed, without eyes—Leptopsylla.

5. Distinction between pulex and xenopsylla is based on the mesopleural plate:—

Pulex has no vertical bar, Xenopsylla has vertical bar.

Therefore, a flea without combs with vertical bar = Xenopsylla.

But a flea without combs, with antennal groove forming a thickening extending to top of head = Pulex.

Nosopsyllus fasciatus is the common rodent flea of temperate and tropical climates, and the dominant rat-flea of Europe. It will attack man in the absence of rats.

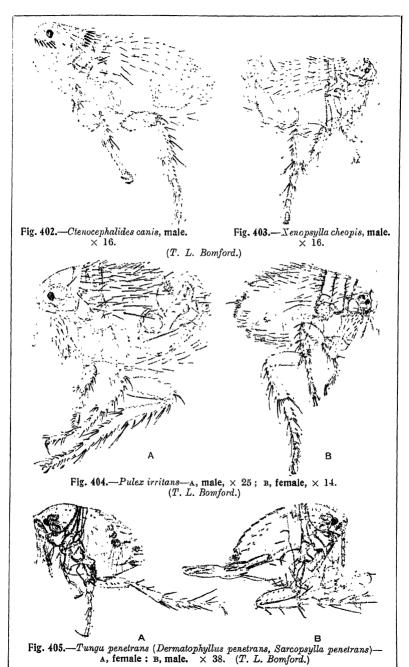
Ctenocephalides.—C. canis and C. felis are very similar and interchangeable between the dog and cat; they may also be found on rats. They attack man readily. (Fig. 402.)

Ctenopsyllus (Leptopsyllus) segnis is the mouse-flea and is also found on rats.

Hoplopsyllus anomalus infests ground squirrels and rats in the western U.S.A., has a pronotal comb, and plays a part in the dissemination of rodent plague.

Pulex irritans, the common human flea, has decreased in Europe enormously

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during the last thirty years but has penetrated many parts of the tropics; it is occasionally found on rats and pigs. (Fig. 404.)

Xenopsulla contains 30-40 species and is essentially an African genus: it. requires a higher temperature to develop, and exists in heated buildings in England, America and Russia. (Fig. 403.)

X. astia (Rothschild, 1911).—In the male the antepygidial bristle is similar to that of X. cheopis, but it is easily differentiated by the shape of the ninth sternite. which, instead of being club-shaped, has the appearance of a ribbon, due to chitinization of its ventral margin. The outer flap of the organs of copulation is narrower than in X. cheopis, and bears fewer bristles. The "tail" of the receptaculum is so strongly widened near the constriction that it is much wider

than the head. The eighth segment has more than 30 bristles on the outer surface. (Fig. 406, 1.)

Xenopsylla brasiliensis (Baker, 1904).— In the male the long dorsal bristle on the seventh abdominal segment in front of the pygidium is placed on a long pedestal. In the female the "head" of the receptaculum seminis is very much wider than the "tail." (Fig. 406, 2.)

X. cheops (Rothschild, 1993).—In the male the ante-pygidial bristle is situated on a short pedestal. The outer flap of the copulatory organs is sole-shaped; its upper edge is more curved than the lower, and bears 9 or 10 bristles on its outer surface, all of them thinner than in X. brasilensis, and drawn out into a long, thin point. The minth sternite has the appearance of a club, the upper side of which is flattened. In the female the "tail" of the receptaculum is much longer than in the preceding species and, near the constriction, is distinctly wider than the "head." (Fig. 406, 3.)

X. cheopis must feed every ten days, except in the adult resting stage and in temperate climates. It may hibernate as an adult and so may remain infected with plague throughout the winter, as occurs in the case of rodent-flea plague in Siberia.

the case of rodent-flea plague in Siberia.

Tunga penetrans (Jarocki, 1838), the "chigger flea" (see p. 688, Fig. 128 and Fig. 405), has a powerfully toothed mandible, a short thorax and slender legs. In the female the spiracles are massed at the hind end of the abdomen. In the early stages it behaves like other fleas, but when the female is impregnated, it attaches itself to the skin, especially of the feet, burrowing deeply with its mandibles until it becomes covered with skin with only the spiracles projecting. When filled with eggs the body swells enormously. When the eggs are discharged the female dies and sloughs away. The egg is oval, about 0.5 mm. in length. A larva emerges in three days, resembling other flea larvæ, but has a chitinous structure on its head, the "egg breaker" with which it slits the egg-shell. Then it feeds on organic matter in dust and passes through two larval stages. A pupa is formed in 14 days. In the second stage the larva spins a silken cocoon within which it easts its skin and becomes pupa. The flea emerges in one week. T. penetrans originated in America, and has long been known in West and South Africa; but only comparatively recently in East Africa and West Coast of India

Importance of fleas to man.—Flea bites may cause severe irritation in some individuals. This is largely an anaphylactic response in persons who are sensitized; subsequent desensitization may take place. Tapeworm eggs are eaten by fleas and encyst in the larva, pupa and adult, e.g., Hymenolepis diminuta of rat and Dipylidium caninum of dog. Endemic murine typhus is normally spread by fleas in the following rhythm:—

rat-rat louse-rat-rat flea-man.

Plague is essentially a disease of rodents spread by X. cheopis and other fleas by the method of "blockage" (see p. 267), which is due to their peculiar type of proventriculus. X. astia can transmit the plague bacillus, but is not nearly so effective as X. cheopis.

Identification.—Three species of Xenopsylla—cheopis, astia and brasiliensis, are ectoparasites of the rat in India. It is not possible to make out the distinguishing features of the three species, unless the specimens are suitably prepared. With the aid of a hand lens, the females can be recognized by the shape of the FLEAS . 1071

spermatheca after the soft parts have been dissolved by caustic potash, or rendered transparent by means of a clearing agent. For the certain identification of the males, a compound microscope is necessary, when it can be seen that the ninth sternite ends in a sharp point in astia, instead of a flattened projection, as in cheopts. The shape of the claspers differs in astia; they are more elongated. These differential characters can only be relied upon in fleas from the Indian area, because in that country only these three species exist.

After a short preliminary treatment with caustic potash, the fleas are treated with alcohol and xylol and placed overnight in a thin solution of balsam in

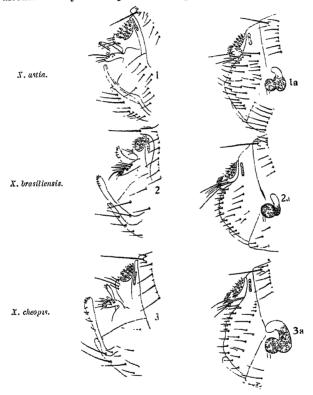


Fig. 406.—Diagnostic characters of Xenopsylla rat-fleas. Magnified. (After Cragg and Hirst.)

X. astia: pygidium of δ; 1a, pygidium and spermatheca of Q; 2, X. brasiliensis: pygidium of δ; 2a, pygidium and spermatheca of Q; 3, X. cheopis; pygidium of δ; 3a, pygidium and spermatheca of Q. Note shape and size of spermatheca.

xylol. Slides are prepared by coating the specimens with a thin layer of balsam and allowing them to dry overnight in the incubator. The fleas themselves are mounted and orientated on the slide; the insects can then be individually examined under the microscope in rows of five.

Prophylaxis.—To rid cats and dogs of these insects they should be washed with carbolic soap or a strong lather of "vermijelli." Cats that object to water may be powdered with naphthaline or dusted with pyrethrum. The floors of

the house should be washed with a solution of naphthaline or benzene. An emulsion of petroleum which will kill fleas when diluted with water, 1 in 20 or more, may be made from soft soap and ordinary petroleum, 3 parts of soap being melted by heat in 15 of water, and 70–100 parts of oil added while still hot, with much shaking and stirring. The final mixture should be white and creamy. For destruction of fleas by DDT, see p. 234.

The irritation of flea-bites may be allayed by the application of 1 in 20 carbolic. The best repellents for fleas are dimethyl phthalate, Rutgers 612 and indalone.

Rat flea survey.—This consists of collecting information on an abundance of fleas and identifying the species at different seasons. Single rats should be caught alive and kept under observation. Fleas should be collected, counted and examined. Rats must be kept apart, for if two are together they will fight and interchange fleas. The rats are killed so as to preserve all their fleas. The trap should be put into a white bag in a chamber filled with cyanide gas, which kills rat and fleas together. The fleas should be mounted in pure carbolic. Record should be kept of the species and sex of the rat, the species and numbers of fleas present.

Flea-index = number of fleas per rat, and is used in making surveys of plague.

SECTION B.—CLINICAL PATHOLOGY

I.—CLEANING SLIDES

NEW slides are suitable for making blood-films, but only when superficial grease has been removed by breathing on them and rubbing briskly with a clean hand-kerchief.

Slides which are dirty or have previously been used should be boiled in soapy solution for about half an hour, then washed in several changes of water, dipped in methylated spirit, and polished with an old linen cloth.

Cover-slips and slides are apt to become frosted when kept for long in the tropics; in order to prevent this they should be stored in spirit.

II.—CARE OF MICROSCOPES AND GLASS WARE

In the tropics, especially where the wet-bulb temperatures are high, fungi are apt to overgrow the lenses of optical instruments. They may even etch or stain the glass and ruin the lenses. Of the fungicides, sodium ethylmercurithiosalicylate is most effective when incorporated in concentration of 0·2 per cent. in a black lacquer which is used for coating the interior metal surfaces of optical instruments. The aim of the manufacturers has been to improve the sealing of instruments and by employing a desiccant to render the use of fungicides unnecessary.

The microscope, when not in use, should be protected by a cellulose acetate hood, similar to those used in biological laboratories. The hood is made sufficiently high to include a microscope supported by a small wooden table, under which is placed a container with calcium chloride to maintain dryness. The edges of the hood are made air-tight by cementing with acetone. The cylindrical shape of the hood is achieved by attaching three wire hoops to the inside with adhesive tape. The hood stands in a wooden box having a circular groove $\frac{1}{4}$ in. wide and $\frac{1}{2}$ in. deep, containing metallic mercury, which forms an air-tight joint, but is not sticky, like petroleum jelly. This can be supplemented

by rings of soft rubber hose tacked on to each edge of the groove and which makes a closely fitting additional joint into which the hood may be slipped (White, 1946).

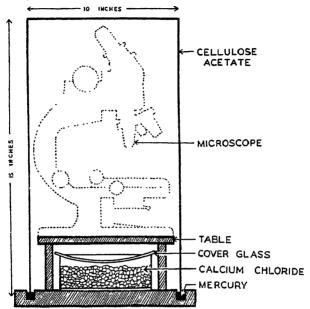


Fig. 407.—Cellulose acetate hood for protecting precision instruments in the tropics. (Courtesy of $Tropical\ Agriculture$.)

III.—METHODS OF PREPARATION OF BLOOD-FILMS THIN FILMS

A drop of blood, obtained by pricking the cleansed finger or ear-lobe, is taken on to the end of a glass slide, without exerting any undue pressure, and avoiding contact with the skin. The drop thus obtained is impinged upon a second slide

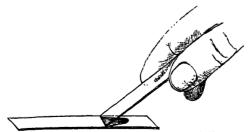


Fig. 408.—Method of spreading a blood-film.

about $\frac{3}{4}$ in. from the end, and the blood permitted to spread evenly. The spreading slide should be pushed, at an angle of 45° , to the opposite end of the horizontal, leaving a thin and evenly-spread film which should then be allowed to dry. (Fig. 408.) An angle of less than 45° makes a thin, and one greater than this, a thicker film. (Figs. 409, 410.)

¹ Blood from the ear is not so satisfactory as that obtained from the finger.

A lancet-pointed hare-lip pin is a satisfactory instrument for pricking the

finger.

Films for differential cell count should be prepared by pressing unevenly upon the slide so as to obtain a wave-like film. By this method the leucocytes congregate at the edges of the waves, thus facilitating enumeration.

THICK FILMS

Ross's thick film is best made by the aggregation of six drops of blood on a slide within an area 5-7 mm. in diameter, which is then spread into an even layer. After dehæmoglobinization with water, the resulting film is dried in air. It should then be stained with Leishman's or Giemsa's stain, as detailed at p. 1076.

Distortion of blood protozoa and leucocytes in such a film can be obviated by use of stains in isotonic solution. The stain should be buffered to pH 6.6 to 7.0. Retention of some of the hæmoglobin is advantageous as it provides a pale yellow contrast background.

Field's thick film.—The blood-drop should be about the size of a sixpence and thin enough to see the hands of a watch through it. The films should be dried and stained when fresh.

Two solutions are necessary, both isotonic and adjusted to pH 6.6:

Solution 1	Solution 2
Methylene blue 0.8 grm.	Eosin l grm.
Azure B 0.5 grm.	Disodium hydrogen phos-
Disodium hydrogen phos-	phate (anhydrous) 5 grm.
phate (anhydrous) 5.0 grm.	Potassium dihydrogen phos-
Potassium dihydrogen phos-	phate (anhydrous) 6.25 grm.
phate (anhydrous) 6.25 grm.	Distilled water 500 ml.
Distilled water 500 ml.	

The dye solutions are stood for twenty-four hours and filtered. Staining is performed by dipping the film for one second in solution 1, rinsing in water till the stain ceases to flow, then dipping for a similar period in solution 2, rinsing in clear water and placing in a vertical position to dry.

There is some difficulty in differentiating younger forms of tertian and quartan from subtertian malaria parasites by these methods, such details as Schuffner's dots being usually invisible. They are, however, very useful for demonstrating parasites in scanty infections, especially rings and gametocytes, and also spirochætes of relapsing fever and trypanosomes when these, as so often, are scanty (see Plate III, 2, p. 37).

Films for demonstration of filarial embryos.—An even larger-sized drop should be taken (20 c.mm.) and spread so as to occupy an area of $\frac{1}{2}$ sq. in. (Fig. 410.) For this purpose the finger should be pricked with a broad-pointed needle and the surface of the slide dabbed with four good-sized drops. The film is allowed to dry, protected from dust (especially from cotton fibres, which may simulate microfilariæ), dehæmoglobinized with water, and stained in a dilute watery solution of fuchsin (5 drops to 150 ml. distilled water), then examined wet under a low power of the microscope.

SKIN SCARIFICATION

Van den Berghe and Chardome (1951) describe an easier and more accurate method of diagnosis of malaria and filariasis by skin scarification smears.

A site is superficially cut so that little bleeding takes place. Finally the scarified area is squeezed between the thumb and forefingers. The dermal capillary blood then obtained is spread either as a thick or thin film on a slide, is stained and examined in the usual way. The microfilarize of Mansonella ozzardi,

D. perstans, D. streptocerca, W. bancrofti, W. malayi, L. loa and O. volvulus are readily found. It is claimed also that a higher percentage of malaria infections is revealed by this method than by examination of thick films.

PREPARATIONS FOR THE STUDY OF FRESH BLOOD

A small drop of blood should be taken upon a clean slide, inverted, and allowed to come into contact with a clean cover-slip upon filter-paper. If no pressure is used, the blood spreads out evenly, the corpuscles tending to congregate round the periphery while the centre remains clear. The preparation may then be ringed with vaseline, and the blood-cells or contained parasites studied under a 1½-in. lens. For living cells (vital staining), a vaseline ring or square of the size of a cover-slip is made upon a clean slide. Then a solution of 0.85 per cent. NaCl with 1 per cent. sodium citrate tinted with methylene-azur, gentian-violet,



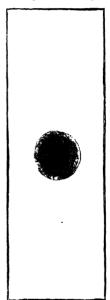


Fig. 409.—Successful thin blood-film.

Fig. 410.—Thick blood-film.

or methyl-green, is taken up in a capillary pipette, together with an equal volume of blood. After mixing, a small drop is placed in the centre of the vaseline ring and immediately covered with the coverslip and pressed down.

Thédan blue (Simons)¹ is a mixture of saponin and methylene blue and is a hæmolytic and at the same time a staining agent with two-fold instantaneous action. It is employed by mixing blood and stain in wet preparations, examined by transmitted light, or by dark ground illumination, or for ordinary films. It is useful particularly when parasites are scanty in the blood, cerebro-spinal fluid or lymph gland material. For identification of trypanosomes or spirochætes it is advantageous as these organisms assume a red colour and with hemolysis of the red blood corpuscles become conspicuous. For malaria parasites crescents are clearly shown. The use of this stain is recommended especially for field work when intensive surveys are undertaken.

¹ From Negociateur A.G., Münchenstein, Switzerland.

IV.—STAINING BLOOD-FILMS FOR BLOOD PROTOZOA AND DIFFERENTIAL COUNT OF CELLS

Leishman's method.—For this method no preliminary fixation is required.

Preparation of stain from the powder is made with 0·15 per cent. solution of methyl-alcohol (acetone-free). In the tropics amyl alcohol is preferable, as it does not evaporate so readily. The powder is placed in a glass mortar, a quantity of methyl-alcohol added, and then ground down with a pestle until the alcohol is saturated. The fluid is decanted off into a clean bottle and a further fraction of methyl-alcohol added to the residue in the mortar, which is again ground down until as much as possible is dissolved. This process is repeated until the whole of the powder is in solution, and sufficient methyl-alcohol is finally added to make up the required volume.

Staining.—1. Select the most suitable part of the blood-film and place a grease-pencil mark on each side, about 1 in. apart—a method which, in staining large batches, results in great economy.

2. Cover the selected part with stain

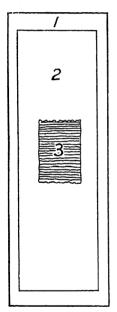


Fig. 411. — McKay's method of staining flagellated body.

1, Slide bearing freshly-made blood-film; 2, pad of damp filter-paper; 3, size of opening showing blood-film and forming with the opposing slide an hermetically sealed damp chamber. by means of a pipette, and leave for a minute, taking care that it does not dry. 3. Dilute the stain 1 in 4 with distilled water, *which must not be acid in reaction* (fresh rain-water may be used), and allow to act for a further 5 mins. (See Tribondeau's test, p. 1077.) 4. Wash off the stain with distilled water and leave a drop on for a minute to differentiate; then place in a sloping position to drain.

For permanent preparations, Leishman-stained slides must not be mounted in Canada balsam, as they rapidly fade, unless it is neutral in reaction or dammar lac be used; they should be examined, unmounted, direct in cedarwood oil, which can be subsequently removed by xylol.

Giernsa's stain.—It is best to obtain the stain already prepared for use by Grübler. The film must first be fixed in a mixture of equal parts of absolute alcohol and ether for 10-15 mins.

Staining.—1. The film should be covered with a 1 in 20 dilution of the stain (1 drop to 19 drops distilled water), which is allowed to act for 20-30 mins. 2. Wash off the stain with distilled water. Place the slide in a sloping position to drain, or dry with blotting-paper.

Hæmatoxylin and eosin.—This method is employed for studying the finer structure of leucocytes, and especially nuclear changes.

After fixation in alcohol and ether for 10 mins. the film should be stained with Delafield's hæmatoxylin for 7 mins. It should be well flushed off with a good flow of tap-water, and left in a running stream for an equal period in order to "blue." While still wet it should be counterstained with a watery solution (5 per cent.) of eosin for 30 secs., after which it should the property of a print to differentiate.

be thoroughly rinsed in tap-water for another 3 mins. to differentiate.

Methods of staining the flagellated body in malaria.—A sheet of thick

blotting-paper, fenestrated with rows of oblong holes (1 in. by § in.), is prepared. It is then moistened with water, and laid smoothly on a sheet of window-glass.

A patient in whose blood the crescent form of the parasite abounds is selected. A clean microscope slide is breathed upon, and the droplet of gametocyte-containing blood taken up by lightly touching it with the centre of the moistened slide. The blood is now rapidly, and somewhat unevenly, spread out with a needle so as to cover an area of about $\frac{3}{4}$ in. by $\frac{1}{2}$ in. The slide is immediately inverted over one of the blotting-paper cells and pressed down sufficiently to secure thorough apposition of the slip without bringing the blood into contact, either with the moistened paper forming the wall, or with the glass forming the floor of what is now a perfect moist chamber. The remaining paper cells are reapidly covered with blood-charged slides prepared in the same way. They are removed and dried at intervals of from 5-20 mins. and subsequently stained by Leishman's method.

McKay's method.—This is an abbreviated, but more effective method. A thin film of crescent-containing blood is made upon a thin slide (1 mm. in thickness, so as to be easily focused through a $\frac{1}{6}$ -in lens). The wet film should be breathed upon and then placed face downwards upon a second slide covered with a small piece of damp filter-paper with a small central opening. The two slides are bound together by elastic bands, thus forming a tightly sealed damp chamber. Exflagellation of the crescent can now be observed under the microscope, and immediately this occurs the film is dried and stained. (Fig. 411.)

Tribondeau's hæmatoxylin test for reaction of distilled water.— Two drops of a saturated alcoholic solution of hæmatoxylin should be added to a test-tube half-filled with the water under examination. If it be neutral, the purple colour of hæmatoxylin will develop in 2-4 mins.: if alkaline, the colour develops immediately; if acid, it is delayed.

V.—VARIETIES OF BLOOD-CELLS AND THEIR SIGNIFICANCE (Plate XXV)

The average total leucocyte-count, made by a Thoma-Zeiss hæmocytometer, is 7,000 per c.mm. of blood. A rise to above 10,000 indicates leucocytosis, a fall to below 5,000 leucopenia. In a differential leucocyte-count, at least 300 cells should be counted under the $\frac{1}{12}$ -in. immersion lens, and by means of a movable stage the preparation should be moved from side to side, so as not to traverse the same field twice.

Neutrophil polymorphonuclear (or microphage) (12 μ).—Normal proportion, 60–70 per cent.; average, 67. With Romanowsky stains, neutrophil granules usually stain slightly acidophil. Variation in shape of nuclei is due to subdivision of the nucleus from one to four or even more lobes, affording some indication of the age of the cell. Thus, a count of these cells according to the numbers of lobes is an aid to diagnosis known as the "Arneth index." A shift to the left is found in liver abscess, pneumonia, relapsing fever, or, indeed, in any septic process.

The precursor of the polymorphonuclear is a bone-marrow cell, the *myelocyte*, of which mature individuals contain granules and mitochondria.

Eosinophil (12–14 μ):—Little larger than the polymorphonuclear, these cells contain coarse eosinophil granules. Usually, the nucleus has not as many lobes as the polymorphonuclear, two being about the average number ("spectacle arrangement"). The normal proportion is 2–4 per cent.; average 3 per cent. Eosinophils are increased in most helminthic diseases—in ancylostome, dracunculus, and clonorchis infections, 5–10 per cent.; in filariasis and paragonimiasis,

10-20 per cent. (*L. loa* infections possibly 60 per cent.); in schistosomiasis and trichiniasis, 20-60 per cent. of the total leucocyte-count. On the other hand, in ascaris and diphyllobothrium infections there may be no appreciable increase.

Basophil (10–12 μ).—This is slightly smaller than the polymorphonuclear. The nucleus is kidney-shaped, or slightly lobulated. The cytoplasm contains large purple granules which often obscure details of the nucleus. Usual proportion is 0.5 per cent.

Lymphocyte.—This is derived from the lymph-glands and other collections of lymphatic tissue. The lymphoblast contains an oval nucleus, poor in chromatin, with a reticular structure, coarser and more stippled than the myeloblast, and is found in acute lymphatic leukæmia. The normal proportion is 19–30 per cent.; average, 23. The small lymphocyte is $5-8~\mu$; the large $12-15~\mu$, though the latter is assumed to be the immature form. This cell is normally increased after physiological digestion, in undulant fevers, pellagra, typhoid and allied fevers, and relatively also in kala-azar.

Large hyaline, or mononuclear (monocyte-macrophage, and transitional). (16-22 μ).—Normal proportion, 3-8 per cent.; average, 6 per cent. This cell is increased in protozoal diseases—trypanosomiasis and malaria; in the latter it often contains ingested hæmozoin. Should the ear be selected for obtaining blood, it is important that no drop earlier than the third should be used, for it has been shown that these cells tend to accumulate in the capillaries of the ear, if the local circulation is slow. It is now understood that large mononuclears are derived from the spleen and bone-marrow and are not related to the lymphocyte. Therefore "transitional cells" must be regarded as mature mononuclears. The cytoplasm contains fine reddish-blue granules.

The monocyte has to be distinguished from the clasmatocyte. The former originates from the reticulum: the latter from the endothelium. They both have the same morphology, staining reactions, and nuclear structure, as shown by ordinary stains, but in vital staining, the clasmatocytes take up trypan-blue,

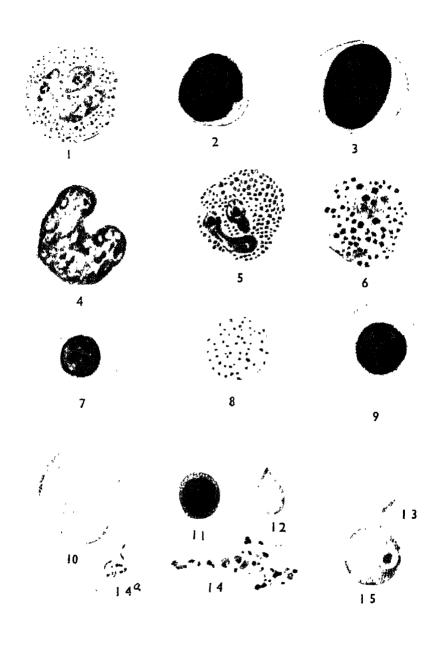
while monocytes do not.

A proportion of 15 per cent. or more of these cells may be considered a reliable aid to the diagnosis of malaria; 10 per cent. may occur in a normal person, and any increase above this calls for further investigation. There is an increase of monocytes during the pyrexia of a primary malarial attack, but a lymphocytosis is associated with relapse.

Leucocytes in childhood.—These are more numerous than in the adult; 12,000 per c.mm. is the average number throughout infancy. The percentage of lymphocytes is doubled, that of the neutrophils is halved. The adult proportion is reached about the tenth year.

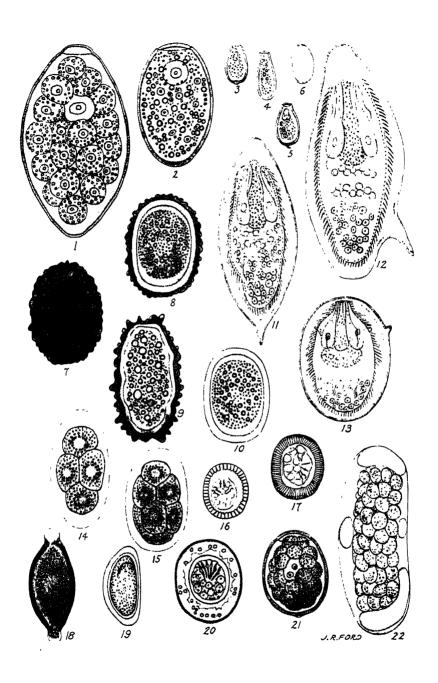
Normal red cell (erythrocyte). $(7\cdot2-7\cdot5~\mu)$.—Normal number, 5,000,000 per c.mm., or more. They are biconcave discs, and therefore thinner in the centre than at the periphery. Erythrocytes are derived from reticulocytes in the bone marrow. The cell membrane of the latter is sticky, so that the cells adhere to one another and to the capillary wall. In the process of maturation this property gradually diminishes. Abnormal red cells are known as ovalocytes, and elongated forms as sickle-cells (p. 27). A total red count, computed from 64 squares on the Thoma-Zeiss hæmocytometer, of under 3,000,000 denotes severe anæmia, and is usually accompanied by changes in the red cells—e.g., in malaria, blackwater fever, sprue, ancylostomiasis and Oroya fever.

Distinctive forms of red cell, reticulocytes, are young red cells formed from normoblasts by fragmentation of the nucleus. They constitute a constant sign



NORMAL AND ABNORMAL BLOOD CELLS

 \times 2,000 (Leishman's stain) Plate XXV



EGGS OF THE COMMONER HELMINTHS FOUND IN MAN

PLATE XXVI

PLATE XXVI

EGGS OF THE COMMONER HELMINTHS FOUND IN MAN. \times 400.

- 1.—Fasciolopsis buski. 2.—Paragonimus ringeri. 3.—Heterophyes heterophyes. 4.—Opisthorchis felineus. 5.—Clonorchis sinensis. 6.—Metagonimus yokogawai. 7.—Ascaris lumbricoides (external aspect). ,, (unfertilized egg). 9.— ,, (decorticated egg). 10.--11.—Schistosoma hæmatobium. mansoni.12.— " japonicum. 13.— 14.—Ancylostoma duodenale. 15.—Trichostrongylus colubriformis. 16.—Tænia solium. 17.- ,, saginata. 18.—Trichuris trichiura. Enterobius vermicularis. 20.—Hymenolepis nana.
- 21.—Diphyllobothrium latum. 22.—Heterodera radicicola (non-parasitic, ingested with vegetables).

of blood-regeneration, and are supravitally stained by cresyl-blue. They are larger and stain more lightly than mature red cells and their stroma contains a blue-staining reticulum. In normal blood these cells amount to 1 per cent., but during blood-regeneration they may reach 20 per cent. or more.

Anisocytosis denotes variations in size of red cells; it is found in various conditions of anæmia, especially of the pernicious type. Poikilocytosis denotes pear-shaped distortion of cells, giving the idea of fragmented corpuscles, and is found in anæmic conditions. Spherocytosis denotes increase of thickness as in acholuric jaundice where the cells stain densely.

Megalocytes.—These are red cells of increased size, 7.2 to $7.5~\mu$ in diameter, and abnormal shape, generally associated with microcytes which are red cells smaller than the normal. Megalocytes occur in the blood in the severe anamias of blackwater fever, subtertian malaria, Oroya fever, sprue, and pernicious anamia.

Normoblasts.—These are seen in small numbers in normal blood, and are increased in severe anæmias—e.g., malarial cachexia, blackwater fever, sprue, ancylostomiasis, kala-azar, and Oroya fever—and in severe helminthiasis. The nucleus is sometimes double or bilobed, and the protoplasm of the cell is usually polychromatophilic. Supravital staining shows a well-marked reticulum in the cytoplasm. These cells are generally present in considerable numbers in spleen and bone marrow punctures in kala-azar, severe malaria, visceral schistosomiasis, pernicious and splenic anæmias.

Polychromatic degeneration of red cells.—This is a phenomenon found in subtertian malaria, blackwater fever, and severe anæmia. The term polychromasia denotes degeneration of the red cell, the cytoplasm of which stains light blue; when severe it is generally accompanied by the formation of polychromatic, or basophilic, dots. It is now generally accepted that polychromasia and stippling are both manifestations of reticulation, so that polychromatic cells in a Leishman-stained film and reticulocytes of a supravitally-stained film are considered identical. Polychromasia is found in malaria, Oroya fever, pernicious anæmia, ancylostomiasis, and lead-poisoning. In thick films the depth of colour of the blue background has been found to afford some indication of the extent of reticulocytosis.

Megaloblasts.—These are abnormal nucleated red cells found in severe anæmias of the pernicious type, including some diphyllobothrium infections; their size is sometimes twice that of a normal erythrocyte. The cytoplasm is non-granular and deeply basophilic, the nucleus large and pale, occupying more than half the cell body, which contains no hæmoglobin.

Howell Joly bodies.—These are small blue chromatic dots in the centre of the erythrocyte, and denote nuclear remains.

Cabot's rings.—A central circular ring is frequently seen in erythrocytes in anæmic blood, and considered to represent part of the nuclear envelope.

Demilunes (Sergent).—These are intracorpuscular vacuoles.

Blood-platelets (3 μ in diameter).—These are round, oval, or rod-shaped, according to the viewpoint, but variability in size is a feature of essential throm-bocytopenia. When resting on red cells they may simulate malaria parasites, but there is always a clear zone due to surrounding pressure (Plate XXV, Fig. 15). When drawn out in making the film they may simulate a trypanosome. They are generally found in masses or in strings, are coated with adhesive substance, and cling to any stationary object. Their function is connected with blood clotting.

VI.—MICROSCOPICAL EXAMINATION OF THE FÆCES AND FOR EGGS OF INTESTINAL PARASITES

The eggs of tapeworms, with the exception of Diphyllobothrium latum, and threadworm (Enterobius vermicularis) (Plate XXVI, 19) are rarely found in the stools, as these parasites do not, as a rule, part with their eggs until the segments of the former, or the entire body of the latter, have left the alimentary canal. Occasionally, the eggs of hepatic and intestinal parasites, such as Schistosoma hæmatobium, S. mansoni, S. japonicum (Plate XXVI, 11, 12, 13), Clonorchis sinensis (Plate XXVI, 5), Fasciola hepatica, Fasciolopsis buski (Plate XXVI, 7), Heterophyes heterophyes (Plate XXVI, 3), and of rarer helminths, are encountered.

The microscopical examination of fæces for eggs is by no means difficult. Place on the slide a minute portion of the suspected fæces, the size of a hempseed, and apply the cover-glass, gently gliding it over the slide so as to spread out

the mass in a thin, fairly uniform and transparent layer.

The points to be attended to in the identification of eggs are size, shape, colour, thickness, roughness, smoothness, and markings on the surface of the shell; the presence or absence of yolk spheres, of a differentiated embryo, or, in the cestodes, of the three pairs of embryonic hooklets; the existence of an operculum in certain trematodes and in the broad tapeworms (*Diphyllobothrium*). Eggs of the same species of parasite vary slightly, but are in every instance sufficiently stable and definite for correct diagnosis.

Of the three common nematodes—Trichuris trichiura (Plate XXVI, 18), Ascaris lumbricoides (Plate XXVI, 7), and Ancylostoma duodenale (Plate XXVI, 14)—the eggs of the first are the most frequently met. Those of T. trichiura occur sometimes in enormous numbers, as many as six or eight speciments being visible in one field of an inch-objective. They form rather striking objects under the microscope. They are oval, measuring 51 to 54 μ by 22 μ , the ends of the long axis of the oval being slightly pointed, and tipped with a little shining projection or plug. Their general appearance suggests an elongated oval tray, the projections at the poles of the ovum representing the handles. They are dark brown, sharply defined, doubly outlined, and contain no differentiated embryo.

Eggs of Ascaris lumbricoides are considerably larger (50 to 75 μ by 40 to 50 μ) than those of trichuris. As a rule they are more spherical or, rather, more broadly oval; occasionally they are almost barrel-shaped. Like those of trichuris, they are dark brown from bile-staining, but they are much less sharply and smoothly defined, possessing a coarse thick shell, which is roughened by many warty excrescences. The yolk contents are not always easily made out, nor, when made out, can any indications of embryo or segmentation be discovered. In certain instances the eggs are smooth on the surface, the rough outer layer being almost or altogether absent. In this condition they are unfertilized.

A point of practical importance is that the rough outer layer of the shell of the egg of ascaris is very easily detached, leaving it with a sharp, smooth outline suggesting some other species of parasite. To obviate this, in mounting fæces it is well to avoid too much gliding of the cover-glass over the slide.

Eggs of Ancylostoma duodenale contrast very markedly with both the foregoing, particularly in colour. Trichuris and ascaris eggs are invariably dark and bile-stained; those of the ancylostome are beautifully clear and transparent, measure 55–60 μ by 32–40 μ , and have a regular, somewhat elongated oval form, with a delicate, smooth, transparent shell, through which two, or four, or eight light-grey yolk segments can be distinctly seen. Eggs should be looked for soon after the fæces have been passed; otherwise, owing to the rapidity with which, in favourable circumstances, development proceeds, the embryo may have quitted the

shell and the egg be no longer visible. The eggs of Necator americanus cannot be differentiated from those of A. duodenale with certainty. The eggs of Trichostrongylus colubriformis also resemble those of A. duodenale, but they are relatively larger and contain a fully segmented morula (Plate XXVI, 15).

The eggs of Heterodera radicicola, which have a characteristic appearance (Plate XXVI, 22), have been noted from time to time in the fæces of otherwise normal individuals since their discovery by Kofoid and White in 1919. H. radicicola is a common root-parasitic nematode living in a variety of plants, such as radishes, celery, carrots and turnips; it is therefore apt to be encountered in the excreta of individuals who have ingested these vegetables. Of conspicuous asymmetric appearance and size, 95 μ by 40 μ , it might well be regarded in human fæces as an indication of nematode infection of the intestinal canal. A feature of the egg is the presence of two highly refractile, flattened, bluishgreen globules at the poles of the embryo. As a rule they are kidney-shaped, and can pass uninjured through the alimentary canal.

The eggs of the cestodes may be distinguished from those of the nematodes and trematodes by their circular outline and, as a rule, by their smaller size.

The eggs of T. saginata and T. solium, which are indistinguishable from one another, are provided with a single brown striated outer membrane, which encloses a ciliated six-hooked onchosphere (Plate XXVI, 16, 17). On the other hand, Hymenolepis nana eggs (40 μ) have two transparent membranes (Plate XXVI, 20). Individual eggs of T. saginata are more ovoid than those of T. solium, and measure 30 μ in diameter. Eggs of Diphyllobothrium latum (70 μ by 45 μ) are translucent, oval and provided with an operculum (Plate XXVI, 21).

A simple method of counting hookworm eggs (Wilkins).—A thick slide, 75 mm. by 25 mm. by 1.7 mm., is cut into three equal pieces. The two end portions are cemented with Durofix to the ends of another slide, leaving a space about 25 mm. square, over which another slide about 20 mm. long is eventually laid, enclosing a space of more than 1 ml. capacity. A 1 ml. pipette, graduated in hundredths, is cut into five short lengths, each containing 0.2 ml. Then, a piece of galvanized wire, which will fit the bore of the pipette, is cut into pieces 4 mm. long, one end of each being bent over in the form of a handle, and the other end being filed off square.

The stool is stabbed with a piece of pipette until this is filled to the 0·1 ml. mark. It is pressed down and twisted, the excess being wiped off. The fæces are pushed out with a piece of wire on to the prepared slide with 0·9 ml. of saturated salt solution. Glycerine is then added slowly from a heated graduated pipette; the fæcal emulsion is covered with the top slide and put aside for 30 mins. to permit eggs to float up. All eggs in the area covered by the emulsion are counted. The result, multiplied by 10, gives the number of eggs in each ml. of stool.

Methods of concentrating helminth eggs.—Clayton Lane devised a technique, known as the "flotation method," which is accurate and useful in the mass diagnosis of ancylostome and, to a certain extent, of other helminth infections. The eggs are collected from 1 ml. of fæces by "direct centrifugal flotation." The aim of the apparatus is to keep fixed upon the centrifuge tube a square glass cover which will collect the floating eggs, and which is held in place by a cover-slip of such a shape as to prevent movement and leakage, and yet permit ready removal of the cover for direct microscopical examination, thus making the area of collection and examination identical. (Fig. 410.) The centrifuge tube is a glass cylinder, $4\frac{3}{4}$ in long by $\frac{1}{2}$ in in internal diameter, closed at the bottom, and with the mouth ground off flat at right angles to the long axis of the tube. The cover is held in position during centrifuging by a cover-slip. The centrifuge is fitted with an axial tachometer, which records the speed at

which the instrument is being revolved. The centrifuge tube is suspended in a metal bucket of $1\frac{1}{2}$ in. internal diameter. Two such buckets are employed, each containing a centrifuge tube, fitted at the upper ends with metal prongs which hold the glass overslips in position. Fæces (1 ml.) are first disintegrated by vigorous shaking in water in a closed tube, and centrifuged for one minute at 1,000 revolutions; the supernatant fluid is decanted, and a solution of salt of a specific gravity of 1,150 added, and centrifuging is repeated for thirty seconds at 1,000 revolutions; the tube should be filled so that the saline lies in contact with the under-surface of the cover-clip. The eggs adhere to the under-surface of the glass, which is carefully removed and examined as a "hanging-drop" preparation.

Direct centrifugal flotation gives a greater and more reliable concentration

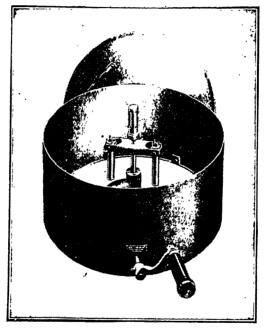


Fig. 412.—Clayton Lane's contrifuge. Greatly reduced. (As supplied by Messrs. R. B. Turner & Co.)

than any other method; the examination area is about $\frac{1}{2}$ sq. in., and the whole process is carried through in a few minutes.

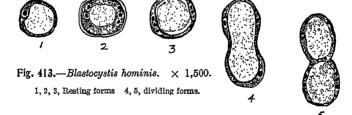
Zinc sulphate centrifugal flotation for concentration of helminthic ova and protozoan cysts (Faust's method, modified by Watson).—For this method, which is highly recommended, the following technique is employed:—A sample of stool, the size of a pea, is placed in a glass centrifuge-tube and broken up to form a fine suspension in distilled water. It is then centrifuged for three minutes at 1,500 revolutions per minute, using an ordinary laboratory centrifuge with a radius of $5\frac{1}{2}$ in. Supernatant fluid is then removed and the process repeated until it is clear. Zinc sulphate solution (33 per cent., sp.G. 1·18) is poured into the tube and the packed sediment is broken up into a uniform suspension. Then a chemically clean circular cover-slip, of slightly greater diameter than the glass

tube, is smeared on one side with a thin film of Mayer's egg medium (white of egg 50 ml., 50 ml. glycerine, salicylate of soda 1 grm., shaken well together and filtered) and pressed firmly on top of centrifuge tube. The suspension is again centrifuged for three minutes at 1,500 revolutions per minute. The cover-slip is carefully lifted off the top of the tube and placed, prepared-surface downwards, on a drop of Weigert's iodine solution on a slide.

Simple flotation method (Hung).—Two grammes of fæces are carefully rubbed up with a glass rod and saturated salt-solution; the mixture is poured into a watch-glass or wide tube, which is filled to the brim. A slide, or cover glass, is placed in contact with the fluid and allowed to remain for ten minutes. When ancylostome eggs are present they will be found adhering to the under-surface of the slide or cover-glass.

Aex method (Faust's method simplified).—In the Aex method of Loughton and Stoll 56 ml. of tap water are placed in a Stoll flask and 4 ml. of fæces, emulsified in water, added. The whole is vigorously shaken with glass beads to produce a homogeneous product. 1.5 ml. of this is placed in a 15-ml. centrifuge tube and to this are added 3.5 ml. of 20 per cent. hydrochloric acid. After stopping with a rubber plug the mixture is shaken for one minute then put aside. Next 5 ml. of a mixture of ether and xylol in equal parts are added and the whole is again shaken for one minute and centrifuged at 1,800–2,000 r.p.m. for two minutes. The material collected on the walls of the tube is carefully removed by a thin piece of wood, the supernatant fluid is poured off and one drop decinormal NaOH added to the deposit. Some of this is removed by a capillary tube and examined. This method is best for Ancylostoma, Trichuris and Ascaris eggs and for Strongyloides stercoralis.

Fülleborn's method for detection of schistosome eggs in the fæces.—The diagnosis of intestinal schistosomiasis (S. mansoni and S. japonicum) by detection of the eggs in the fæces is not always easy. Fæces of the volume of a hazel-nut are placed in a conical glass, carefully rubbed up with a glass rod and a little $2\frac{1}{2}$ per cent salt-solution, and put away to settle, in the dark, for five minutes. The solution is poured off from the sediment, and the process repeated two or three times



The schistosome eggs remain in the sediment, which is flooded with distilled water at 120° F. and exposed to a bright light.

The miracidia now escape from the eggs, and can easily be detected with a hand lens, particularly against a dark background. On adding a few drops of perchloride of mercury solution, they are killed off and are found in the sediment.

Microscopical examination and recognition of various elements in the fæces.—Blastocystis hominis (Fig. 413).—Sometimes during examination of fæces, a yeast-like organism—Blastocystis—simulating an amedic cyst, but less refractile, is encountered. (Plates XXIII, XXIV.) Each cell contains a large central vacuole, while the cytoplasm is reduced to a thin layer in which are

situated one or two small iodophilic nuclei at each pole. The cytoplasm contains refractile globules of volutin which should not be mistaken for the nuclei. Blastocystis multiplies by gemmation and rapidly increases in culture media such as are suitable for E. histolytica, unless dextrose has been added. The organism varies a good deal in size and shape; single cysts measure from 5–20 μ in diameter. This organism has no pathogenic significance.

Muscle-fibres, derived from meat, practically always occur in the stools, and are recognized by their cross-striation. When present in large numbers they indicate defective intestinal digestion. (Fig. 414, 2.)

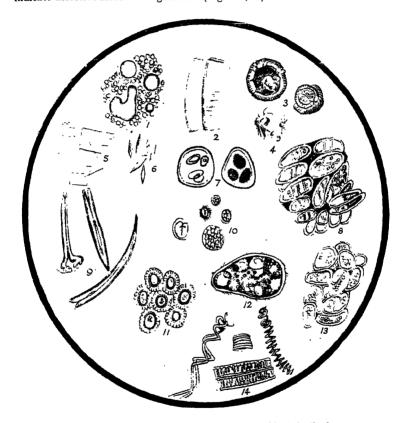


Fig. 414.—Microscopic appearance of common objects in the fæces. \times 800 diam.

Casein and fat droplets: 2, muscle-fibres; 3, soap crystals; 4 crystalline fatty needles; 5, cholesterin crystals; 6, Charcot-Leyden crystals; 7, truffle spores; 8, portions of husks of cereals; 9, hairs of wheat grain; 10, spores of fungi: 11, cells from pericarp of peas, 12, parenchyma of beans; 13, endosperm of rice, 14, vegetable spirals.

Connective tissue, derived from meat, somewhat resembles mucus; it is distinguished by striation, which disappears on addition of acetic acid. When it is present in large masses, defective gastric digestion may be inferred. Elastic fibres have no significance.

Starch granules, derived from fruit and potatoes, are stained blue by iodine solution. They vary in size and shape, according to the food from which they are derived. Well-preserved granules with concentric markings are seldom seen. They are often enclosed in a cellulose covering, and can readily be recognized, except those from peas and beans, which roughly resemble tapeworm eggs.

Excess of starch is pathological, and such a stool is usually acid and shows signs of gas-bubbles, fermentation, and yeasts. The iodine test may be applied to ascertain the extent to which starch has been digested. A blue colour indicates unchanged granules: red, that digestion has begun.

Detritus derived from fruits and vegetables is easily recognized by spiral ducts, areolar tissue, vascular bundles and pigment cells.

Neutral fats, derived from fat, are recognized as colourless, highly refractile droplets, or sometimes as irregular bile-stained masses which are stained by Sudan III and are insoluble.

Fatty acids, derived from fat, occur as sheaves of colourless acicular crystals, which melt on being warmed and dissolve in ether. (Fig. 414, 4.)

Soaps from the fat of food occur as greasy-looking amorphous masses, or sometimes as needles, which are thicker and not so long as those of the fatty acids. They may be colourless, or stained with bile-pigments. Insoluble in ether, as are fatty acids, they do not melt on being warmed. If the film of fæces on a slide is treated with acetic acid and heated fatty acid crystals will separate out. (Fig. 414, 3.)

Fats may be distinguished from mucus or from vegetable material by the following rough test: prepare a smear of the stool on a slide, put on a cover-slip, and press the latter down on to the smear: should the material be of fatty composition, the cover-slip will remain in place; if vegetable detritus or mucus, it will spring back when pressure is released. (Fig. 414, 7.)

In a normal stool, fat is present almost entirely in the form of amorphous masses of soap, less often as crystals. Neutral fat is normally absent.

Mucus occurs as transparent shreds, sometimes bile-stained. It has always a pathological significance and, when it contains leucocytes and epithelial cells, indicates intestinal ulceration.

Intestinal sand.—Sand grains in the fæces of persons who live in deserts are extremely frequent, but sand-like material is a pathological product sometimes present in diverticulitis.

Charcot-Leyden crystals are frequently found in stools containing entamæbæ. (Fig. 414, 6.) These crystals have a chemical connection with eosinophil cells; they are therefore most evident in diseases with an eosinophilia. Originally seen in leukæmic blood, they are recorded in smear preparations from periarteritis nodosa, trichiniasis, intestinal infections, and in localized collections of eosinophils in nasal polypi and skin blebs.

Pseudo-parasites.—It frequently happens that orange-pulp is mistaken for trematodes, banana fibres for small tapeworms, pieces of cotton-thread and celery for Enterobius vermicularis, Ancylostoma duodenale, etc. In microscopic diagnosis numerous objects may be mistaken for helminthic eggs, and it is important that the tropical worker should be able to recognize various articles of diet as they appear in the stools. The spores of truffles, which occasionally are seen in the fæces, may be mistaken for eggs of Ascaris lumbricoides, owing to their size (42–66 ν) and rough surface. (Fig. 414, 7.) The spores of mushrooms have a somewhat similar appearance. Pollen grains of plants and spores of fungi have given rise to difficulties, in spite of their characteristic

appearance; pollen of conifers is often met in the stools of people living near pine forests. All these spores are globes with a reticulated surface which can be made out on careful focusing. (Fig. 414, 70.) Occasionally cheese-mites and their eggs may be seen in the fæces.

Demonstration of protozoa in fæces.—It is difficult to make out the nuclear details of the intestinal protozoa and their cysts in a fresh state. Weigert's iodine solution (iodine, 1 part, pot. iod., 2 parts, water, 100 parts), has a special affinity for nuclear structure, renders the details much more evident, and assists in their recognition. (Plate XXIV.)

Methods of concentration of protozoal cysts in fæces.—Yorke advocated the following method of concentration, especially applicable to cysts of Entamæba histolytica:

A mass of fæces is ground up with water in a small mortar and the emulsion shaken with 500–1,000 ml. of water, poured into a tall glass cylinder, and allowed to stand for fifteen minutes, to permit the coarser fæcal material to settle. The supernatant fluid is withdrawn and centrifuged, and the deposit is shaken up with a solution of cane-sugar of specific gravity of 1,080 and again centrifuged quickly. This procedure results in the separation of cysts from the remaining fæcal material. The fæces are precipitated and the cysts left floating in the supernatant fluid, which is withdrawn, diluted with about four times its volume of water, and again centrifuged at high speed. By this means a small deposit is obtained, consisting of great numbers of cysts in a relatively minute quantity of fæcal material. The deposit is then washed several times with water to get rid of all traces of sugar and the majority of the remaining bacteria.

VII.—EXAMINATION OF THE URINE FOR EGGS OF SCHISTOSOMA HÆMATOBIUM

The miriadiascope (optical arrangements originally designed by Gorman) consists of a specially constructed wooden rack painted dull black to hold centrifuge tubes and a hand lens 1 in. in diameter and of $2 \cdot in$ focal length which gives sufficient magnification to view the miracidia swimming about in the water. The value of this instrument is two-fold.

(1) The procedure is relatively simple and an opinion as to the presence of schistosomiasis can be given in an outstation clinic or even during school inspection.

(2) It is employed in determining the viability of schistosome ova.

For use the terminal portion of the urine is collected and stood for 30 minutes after which the upper part is decanted, leaving sufficient to fill a centrifuge tube. This is centrifuged at low speed and the liquid is gently drawn off; 5 ml. of water are added to the deposit. The tube is then inserted into one of the holes provided in the rack. Hatching is usually complete within 20 minutes but may be delayed up to 40. If viable ova are present in the urine they hatch and the miracidia can be seen swimming around actively (Meeser, Ross and Blair, 1949).

Figures in bold type indicate the principal reference

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